Update on the Treatment of Systemic Lupus Erythematosus: Therapeutic Highlights from the Sixth International Lupus Conference

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Key words: systemic lupus erythematosus, cyclophosphamide, mycophenolate mofetil, biologic agents

IMAJ 2002;4:71-73

The sixth international systemic lupus erythematosus conference took place in Barcelona, Spain, and was organized by Munther Kamashta. More than 400 abstracts were presented at the meeting and were published in a special issue of *Lupus* [1]. Several centers presented their experience with old therapeutic modalities for SLE including cyclophosphamide, anti-malarial agents, steroids, methotrexate and others. New therapeutic modalities are shown in Table 1. The role of high dose cyclophosphamide, stem cells transplantation and new biologic agents was also reported. We summarize the presentations that focused on both the traditional and new therapeutic modalities of SLE.

Cyclophosphamide

Cyclophosphamide remains the standard therapy for patients with diffuse proliferative lupus nephritis. It may also be effective in severe cases of central nervous system involvement or pulmonary hypertension. Of 22 Mexican SLE patients with neurologic manifestations (refractory seizures, peripheral neuropathy, optic neuritis, transverse myelitis, coma and others), 21 responded to monthly intravenous pulse cyclophosphamide compared with only 7 of 11 patients treated with methylprednisolone (L. Barile). The mean pulmonary artery pressure of 8 SLE patients with pulmonary hypertension decreased from 43 to 28 mmHg following monthly i.v. pulse cyclophosphamide (L. Gonzalez-Lopez).

New therapeutic regimens for the use of cyclophosphamide were reported. F.A. Houssiau for the Euro-Lupus Nephritis Trial Group presented their experience with the use of six pulses, every 2 weeks, of 500 mg cyclophosphamide for lupus patients with proliferative nephritis. This regimen was followed by daily azathioprine. Of the 90 patients enrolled in the study, 44 received short-course cyclophosphamide and 46 patients were treated according to the standard protocol. All patients also received three IV pulses of methylprednisolone (450 mg each day) followed by oral prednisone 0.5–1 mg/day. An interim analysis after a mean follow-up period of 33 months revealed no differences between the two groups in the various clinical outcomes tested, including the rate of renal remission, development of renal failure, mortality, and flare of SLE. Eighteen patients in each group achieved complete renal remission. The number of patients who developed serious infections was lower in the group treated with the short regimen, suggesting that low dose cyclophosphamide is a safe and efficacious treatment for proliferative lupus nephritis.

An extended follow-up study (mean 11 years) of 82 patients with proliferative nephritis followed at the National Institutes of Health found the combination

Table 1. New therapeutic modalities for SLE

Therapeutic agent	Therapeutic regimen
Short-course cyclophosphamide	6 IV pulses of 500 mg every 2 weeks, followed by azathioprine
Immunoablative high dose cyclophosphamide	IV 50 mg/kg of cyclophosphamide for 4 consecutive days
Mycophenolate mofetil	2 g/day
Stem cell transplantation	High dose cyclophosphamide, followed by autologous hemopoietic stem cell (CD34) infusion
Biologic agents	
Anti-IL-10	20 mg for 21 days
Anti-CD 40	Single dose
LJP 394	100 mg weekly
Leflunomide	20 mg daily
Prasterone	200 mg daily

SLE = systemic lupus erythematosus

of cyclophosphamide with pulse methylprednisolone to be as effective as cyclophosphamide alone in an intention-to-treat analysis. However, among patients who completed the protocol, the combination of both agents was associated with a significantly lower rate of patients who had 50% or 100% increase in creatinine compared with patients treated only with cyclophosphamide, indicating that the combination of cyclophosphamide and methylprednisolone seems to be superior to cyclophosphamide alone.

Michelle Petri reported the Johns Hopkins experience with immunoablative high dose cyclophosphamide for refractory SLE [2]. The treatment protocol was based on 4 consecutive days of 50 mg/kg/day cyclophosphamide. Of the 14 patients included in the study, 9 had renal disease, 3 had severe neuropsychiatric disease and 2 had refractory cutaneous lesions. Of the nine patients with renal involvement, four had complete remission, three showed a partial response and two did not respond to the therapy. One patient with ataxia and another with pyoderma gangrenosum responded completely. One patient with encephalopathy had a partial response, but he developed membranous nephritis. The data indicate that some patients with refractory SLE may achieve partial or complete remission following high dose cyclophosphamide.

Mycophenolate mofetil

Recent studies have found MMF, a reversible inhibitor of inosine monophosphate dehydrogenase, to be effective in patients with refractory lupus nephritis. Eighteen SLE patients refractory to immune suppressive therapy received MMF at St. Thomas' Hospital (UK). Seven patients had active renal disease. Three patients discontinued the therapy due to gastrointestinal or skin side effects. The therapy was associated with a significant reduction in SLEDAI (from 12.8 to 6.2), 24 hour protein excretion (from 4.0 to 1.2 g) and prednisolone dosage (from 19 to 12.8 mg). No significant change was observed in the levels of complements and serum creatinine.

A study from China found MMF to be less toxic and as effective as cyclophosphamide in a group of 90 SLE patients with various clinical manifestations including renal, pulmonary, CNS, and or vasculitis.

Six centers participated in the Renal Association Glomerulonephritis Study group, UK. Patients with proliferative lupus nephritis who were not treated with cyclophosphamide were enrolled in the study and received MMF 2 g/day, with a reducing dosage of prednisolone. Six months and a year after enrolment, MMF therapy resulted in a reduction of proteinuria (3.4 to 1.1), BILAG score (20 to 6), and improvement in serum albumin (28 to 38) and C3 (0.6 to 1.08).

Taken together, the available data suggest that MMF appears to be effective and safe for patients who failed immunosuppressive agents, as well a first-line modality for proliferative lupus nephritis.

Stem-cell transplantation

Alan Tyndall detailed the principles of stem-cell therapy for autoimmune diseases. This modality is used for refractory cases of SLE in Europe and the USA [3]. Alberto Marmont reported the results of hemopoietic stem-cell transplantation in the USA and Europe. This referred to 22 SLE patients with refractory disease to cyclophosphamide treated with high dose intense cyclophosphamide and autologous hemopoietic stem cell (CD34) transplantation infusion. Nineteen patients were female and their mean disease duration was 18 years. The main clinical manifestations were renal, neurological, cardiovascular and/or vasculitis. Four patients died as a result of thrombotic thrombocytopenia purpura, disseminated intravascular coagulopathy, sepsis and multi-organ failure. Non-fatal complications included sepsis (28%), and fever of unknown origin (17%). The mean SLEDAI score declined from 18 before therapy to 3 at day 100. Only 35 and 13% of the patients had positive anti-nuclear antibodies and anti-DNA at day 100 respectively. The disease-free survival was 35%. At the last assessment, five patients were not taking medications, and eight began new immunosuppressive agents. Although this regimen was associated with significant morbidity and mortality, it may be efficacious in selected severe and refractory cases of SLE.

Biologic therapy

SLE is associated with the secretion of various pathogenic autoantibodies, which are generated by B cells and are T cell-dependent. Stimulation of T cells occurs after the presentation of self-peptides, by the major histocompatibility complex molecule of the antigen-presenting cells, to T cells.

Various biologic agents are currently under investigation or being used in clinical trials for patients with SLE. Those agents are designed to modulate the immune system by affecting cytokine activity, antigen presentation, activation and proliferation of B and T cells.

F. Houssiau reviewed the role of various cytokines in the pathogenesis of SLE and their therapeutic implication. Increased levels of interleukin-10 were found in the sera of patients with SLE and associated with defective T cell regulation of antibody production by B cells. In an open-label study six SLE patients were treated with 20 mg daily of murine anti-IL-10 for 21 days. The treatment was associated with improvement in vasculitic and skin lesions and arthritis. A decrease in the SLEDAI scores and steroid levels was also observed during 6 months of follow-up. Side effects included chills in one patient.

David Wofsy summarized the possible biologic agents that suppress the co-stimulation and proliferation of T cells by APCs. Those agents prevent the interaction of ligands on APCs with receptors on T cells (signal 2 interaction). This

MMF = mycophenolate mofetil

CNS = central nervous system

IL = interleukin

inhibition may lead to anergy, and no proliferation of B cells develops.

Monoclonal antibodies against the CD40 ligand were used to treat patients with SLE. This ligand is found on APCs, denderitic cells and B cells. During signal 2 it binds CD40L to activated T cells. Blocking this interaction may suppress proliferation of B cells. This placebo-controlled study of anti-CD40 included 85 patients. The study was discontinued since it was not found to be superior to placebo.

Inactivation of signal 2 may be achieved by manipulating the binding of B7 ligand (found on APCs) to CD28 (on T cells). Both receptors are upregulated during T cell activation by APCs. CTLA 4 is also expressed on T cells and bind with high affinity to B7. CTLA4-immunogobulin is a fusion of the extracellular domain of CTLA 4 with the Fc portion of IgG1. Treatment with CTLA4-Ig was found to be helpful in mice and in human psoriasis. Treatment of NZB/W mice resulted in improved survival and regression of nephritis. No data are available regarding patients with SLE. Future regimens may include a combination of biologic agents.

LJP 394 is a biologic agent designed to downregulate the production of anti-DNA antibody. It is composed of 4 dsDNA oligonucleotide epitopes attached to an inert triethyleneglycol backbone. LJP 394 binds circulating anti-DNA and cross-links anti-DNA on the surface of B cells. A double-blind placebo-controlled study (90-05 trial) including 230 SLE patients who received LJP 394 was reported by D. Alarcon-Segovia. The anti-DNA antibodies of 89% of the patients enrolled in the trial was found to bind the drug with high affinity. Among these patients, renal flares were observed in 7 patients who received LJP 394 compared with 21 flares in the placebo group. In a subsequent subanalysis, M.D. Linnik found LJP 394 to delay renal flare among SLE patients with creatinine > 1.5. Renal flares were observed in 18% of the LJP 394 treated patients compared to 55% among patients who received placebo.

APC = antigen-presenting cell
Ig = immunoglobulin

Other agents

Case reports found various agents to be effective in cutaneous lesions. This includes dapsone for chronic cutaneous lesions refractory to steroids, anti-malarials, methotrexate for severe bullous eruption, and intravenous immunglobulin for vasculitic skin lesions and for recurrent miscarriages in a patient with SLE and anti-phospholipid syndrome.

Leflunomide

In an open-labeled study, 18 SLE patients were treated with leflunomide 20 mg daily after 3 days of 100 mg daily. Four patients withdrew from therapy due to side effects. A reduction in the SLEDAI scores was observed in nine patients (D.J. Wallace, LA).

Prasterone

In a multi-center U.S. study, 381 patients with mild to moderate SLE were enrolled in a double-blind study of oral prasterone, an androgen analog, or placebo for 12 months. Overall, 66 patients with active disease responded to therapy compared to 49% of the placebo group ($P = 0.005$). Response was defined as improvement in four outcome measures (two disease activity and two quality of life measures). The degree of improvement in disease activity indices was not given and the frequency of SLE flares, among patients who received placebo or prasterone, was similar. Furthermore, no data were available regarding patients who had remission of their disease. This suggests that androgen analogs may have some role in the management of SLE, although its exact efficacy is not clear.

Metabolic effects of prasterone were also reported. Prasterone was associated with a 13% decrease in the levels of high density lipoprotein and total triglycerides with no effect on the levels of low density lipoprotein, which may be associated with an increase in the atherogenic index. The agent was found to increase bone mineral density of the lumbar spine (1.8%) and hips (2.1%). A higher percentage in bone mineral density was seen in post-menopausal women, 3.2% in the lumbar spine and 2.4% in the hips.

Anti-malarial agents

During the last decade there have been reports indicating that anti-malarial agents may improve the lipid profile in patients with SLE. In Mexico (O. Vera), 64 SLE patients were enrolled in a placebo-controlled study of 4 mg/day chloroquine. Six months after therapy began there was a significant increase in the levels of HDL, no difference in the levels of LDL, total cholesterol or triglycerides, and there was a significant decrease in the atherogenic index.

Summary

The studies presented at the conference indicate that new therapeutic agents are effective for patients with SLE. Some of the agents (high dose cyclophosphamide) may be given to patients with refractory disease while others (low dose cyclophosphamide, and MMF) may be used as a first-line drug. The current data on biologic agents are still preliminary and their exact role in SLE needs to be determined.

References

1. Sixth International Lupus Conference. *Lupus* 2001;10:S1.
2. Brodsky RA, Petri M, Smith BD, Seifter EJ, Spivak JL, Styler M, Dng CV, Brodsky I, Jones RJ. Immunoablative high-dose cyclophosphamide without stem-cell rescue for refractory, severe autoimmune disease. *Ann Intern Med* 1998;129:1031–5.
3. Traynor AE, Schroeder J, Rosa RM, Cheng D, Stefka J, Mujais S, Baker S, Burt R. Treatment of severe SLE with high-dose chemotherapy and haemopoietic stem-cell transplantation: a phase I study. *Lancet* 2000; 356:701–7.

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HDL = high density lipoprotein
LDL = low density lipoprotein