Study Identifiers: DI SLE. Auto 2003; NCT 00278538

Study Title: Cyclophosphamide and Rabbit Antithymocyte Globulin (rATG)/Rituximab in Patients with Systemic Lupus Erythematosus

10/29/2015

Cyclophosphamide and rATG/rituximab in Patients with Systemic Lupus Erythematosus: Phase II Trial

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Cyclophosphamide and rATG/rituximab in Patients with Systemic Lupus Erythematosus: Phase I Trial

STUDY SYNOPSIS

Participating Sites:	Northwestern Memorial Hospital
Accrual Objective:	40 participants
Primary Study Objective:	The primary efficacy outcome is overall survival and the proportion of participants who achieve and maintain remission after transplant. Remission is defined according to the RIFLE as duration on no immune suppressive medications except physiologic doses of prednisone (<10 mg/day) or corticosteroid equivalent and or hydroxychloroquine.
Trial Treatment:	Participants will receive high dose cyclophosphamide (200 mg/kg), **rATG (6mg/kg) and rituximab 200mg**, followed by rescue with peripheral stem cells.
Study Duration:	The trial duration will be 5 years.
Study Population:	Participants with systemic lupus erythematosus (SLE) will be enrolled in the study. Participants must be 16 to 60 years of age and must meet at least 4 of 11 American College of Rheumatology (ACR) classification criteria for SLE.

1. Background Information and Scientific Rationale

1.1. Background Information on Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multi-system, inflammatory disorder characterized by the production of antibodies that react with many different self-antigens. Despite differences in presentation, manifestations, and clinical course, the common factor for patients with systemic lupus erythematosus (SLE) is hyper-reactivity of T and B cells to endogenous stimuli.

Currently, in developed countries, mortality from SLE is estimated at 3 per million person-years.[1,2] A number of factors are associated with poor prognosis; these include the presence of renal disease causing an elevation in serum creatinine or urine protein excretion above normal, hypertension, diffuse proliferative glomerulonephritis on renal biopsy, chronic changes on biopsy, lung involvement, a high Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score at the time of first lupus clinic visit, anemia, thrombocytopenia, and antibodies to phospholipids.[1]

Rose's criteria for proof that a disease is autoimmune requires transfer of disease to a person by transfer of antibodies or immune cells from an afflicted individual.[3] Evidence of a suspected autoimmune etiology for most diseases is indirect and based on laboratory evidence of immune responses to self that are quantitatively and/or qualitatively different from a healthy population, and response to anti-inflammatory and/or immunosuppressive therapies. The autoimmune nature of SLE is supported by several observations. First, nephritis may be induced in asymptomatic mice by injection of anti-DNA antibody from mice afflicted by a lupus-like nephritis[4] and occurs in normal mice made transgenic for the heavy and light chains of an IgG antibody to double-stranded DNA.[5] Second, in SCID mice that cannot reject xenogeneic proteins, injection of anti-DNA antibody from patients with SLE induces proteinuria.[6] Third, in 1959, healthy individuals were transfused with 300 mls of plasma from LE positive patients with SLE.[7] There was no observable clinical effect, but the patients developed transient LE cells, which result from phagocytosis of antibody coated nuclei. It is unknown if continued transfusions of SLE plasma could have precipitated clinical disease. Fourth, disease activity for most patients with SLE correlates with serum levels of anti-double stranded DNA (anti-ds DNA) antibody titer.[8] In general, SLE is responsive to immune suppression, indirectly supporting an autoimmune pathogenesis.

1.2. Clinical Classification of Disease Staging

Multiple indices exist to measure or characterize disease activity. Activity instruments include the British Isles Lupus Assessment Group scale (BILAG),[9] Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),[10] Systemic Lupus Activity Measure (SLAM),[11] and the Lupus Activity Index (LAI).[12] The instrument employed depends on institutional and investigator familiarity.

1.3. Underlying Immunologic Mechanisms

SLE is probably a genetically heterogeneous disease influenced by multiple loci. In New Zealand Black / New Zealand White F1 hybrids (NZB/NZW) mice, various mating crosses of lupus prone mice, as well as backcrosses to normal mice have linked murine lupus to 38 different genomic loci.[15] Depending upon the cross-mating strains, different loci with different nomenclature have been identified. Examples of nomenclature for loci associated with SLE are: Lrdm (lpr renal disease modifier), nba (New Zealand Black autoimmunity), Lbw (lupus NZB x NZW), and Sle (systemic lupus erythematosus).[16-22] Murine lupus-like disease is polygeneic with multiple genes (including Sle1, Sle3, Ldrm1, Ldrm2, nba1, nba2, Lbw3) contributing. Some loci are associated with one or more of the following: glomerulonephritis, vasculitis, anti-ds DNA, anti-chromatin antibody, lymphoproliferation, or splenomegaly.

No single gene is sufficient to cause disease in animal studies. This suggests that human SLE is also polygeneic with multiple potential combinations predisposing to SLE. Genetic analysis predicts that many genes are involved in the expression of lupus in humans.[23] Class II molecules, DR2 and DR3, have been associated with lupus in North American whites. Various combinations of SLE-prone genes among different patients may explain why patients with SLE can have highly variable organ involvement and clinical symptoms.

Additionally, it is believed that genetic disposition alone is not sufficient to induce lupus in humans. In monozygotic twins, 30-50% are concordant for disease.[24] The disease is much more common in females than males, with approximately 7:1 ratio of women to men in child-bearing years.[25] A multi-factorial etiology including genetic predisposition, permissive sex hormone status, and environmental interaction are probably necessary for development of clinical disease.

The common thread in disease pathogenesis in humans is T and B cell hyper-reactivity. T cells from patients with SLE provide help to B cells to produce autoantibodies.[26] An unaffected person's peripheral T cells are less than 1% positive for CD69 (a marker of activation), and upon *ex vivo* exposure to a mitogen such as PMA (4Bal Phorbol 12 Myristrate 13 Acetate) more than 80% of the T cells will present CD69 within 4-6 hours. Pretransplant T cells from patients with lupus display the activation marker CD69 in 10-54% of the unstimulated cells and fail to appropriately further upregulate CD69 expression in response to PMA.[27] Fresh T cells and T cell lines from patients with lupus display enhanced TCR-mediated protein tyrosine phosphorylation and intracellular free calcium concentrations.[28,29] Therefore, T cells from patients with lupus may "overshoot" surface mediated signaling events. This is further supported by the observation that expression of second signal molecules such as CD40 ligand are increased on the T cells and B cells of patients with SLE,[30] and levels of soluble CD40L are increased in sera.[31] Lymphocytes from some patients with active lupus also display a Th2 cytokine skewing.[32] In general, Th2

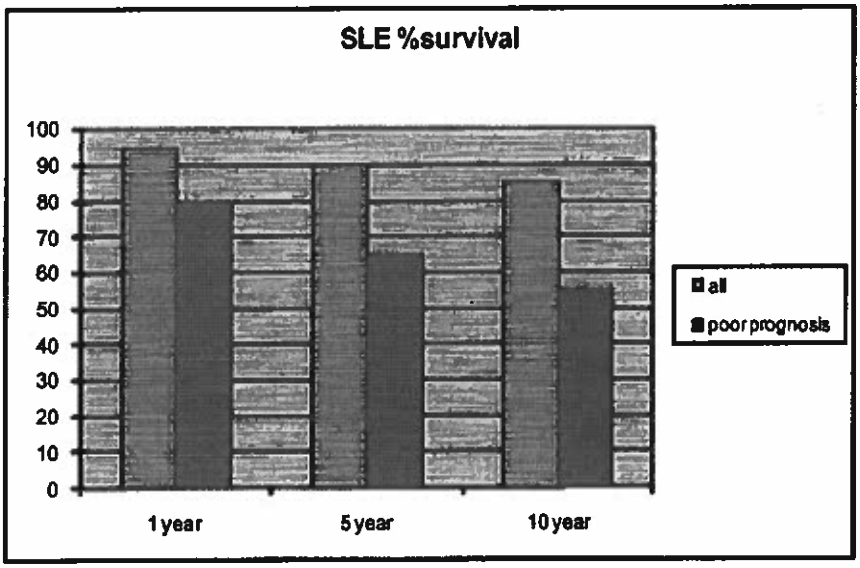
cytokines promote B cell antibody production. The pattern of cytokine expression in SLE cells and patient sera is complex and multiple studies have yielded different results, depending on methods used and characteristics of patients studied.[33] There is general agreement that levels of IL-10 are increased in sera of many patients, and generation of TGF-beta by PBL is significantly lower compared to normal individuals.[34]

The pretransplant T cell receptor CDR3 repertoires are also skewed indicating expansion of reactive T cells.[35] After transplant, these pretransplant T cell hyper-activation abnormalities normalize.[27] Although encouraging, the post-transplant duration of a normalized T cell phenotype is unknown. Analysis of B cell activation, signal transduction and immunoglobulin receptor skewing is yet to be performed on the pre and post-transplant samples.

It appears that T cell stimulation of B cells occurs in the pathogenesis of lupus patients. Once stimulation of B-cells has taken place and anti-self immunity has been stimulated, the memory for anti-self immune responses is retained and reactivation of pathogenic antibodies occurs with greater ease in subsequent relapses.

1.4. Current Therapy

Mortality from SLE has markedly improved due to more aggressive anti-inflammatory and immunosuppressive treatments as well as improved supportive care from dialysis, apheresis, and newer anti-hypertensive and antibiotic medications. For patients with diffuse proliferative glomerulonephritis, 5-year survival in the 1950's was almost zero percent.[28] With introduction of high-dose corticosteroids in the 1960's, the 5-year survival for this subset improved to 25%.[38] Following addition of oral cyclophosphamide and azathioprine, 5-year survival in severe lupus nephritis improved to 40-70%. In the 1980's, introduction of intravenous pulse cyclophosphamide (500-1000 mg/m^2 monthly for six months and then every three months for six months) improved 5-year survival to 80%.[29] More recent therapies for SLE include cyclosporine and mycophenolate mofetil.[40] Twelve-month survival rates and response rates were similar in patients with lupus nephritis (approximately 80%) treated with either daily oral cyclophosphamide for 6 months (followed by daily oral azathioprine for 6 months) compared to mycophenolate mofetil daily for 12 months. The current standard of care in the USA for patients with SLE nephritis that is life-threatening is intravenous pulse cyclophosphamide (500-1000 mg/m^2) per month for six months and then every three months for six months. Despite these advances for high risk SLE, mortality is 20% at 2 years and 35% at 5 years which is an unacceptably high mortality for predominately young women between ages 20 to 30.



1.5. A Summary of Preclinical and Clinical Experience

1.5.1. Preclinical experience with hematopoietic stem cell transplantation

Animal autoimmune diseases that are induced by immunization with adjuvant or self-peptide and adjuvant may be ameliorated by syngeneic or pseudo-autologous hematopoietic stem cell transplantation (HSCT).[41-52] Immunization with adjuvant and either myelin basic protein (MBP) or proteolipid protein (PLP) peptides induces a T cell mediated demyelinating disease, Experimental Autoimmune Encephalitis (EAE). Depending upon the animal model, EAE may be similar to multiple sclerosis (MS) -- monophasic, relapsing-remitting with secondary progression or progressive from onset. In particular, EAE in Swiss Jackson Laboratory/Jackson (SJL/J) mice is a relapsing remitting and secondarily progressive disease. Several investigators have demonstrated cure, decreased relapse rates, or decreased disease severity in SJL/J mice undergoing syngeneic HSCT.[43,45,49,50] Some investigators have reported post transplant antigen specific tolerance suggesting that the HSCT induced tolerance through clonal deletion or anergy of myelin reactive cells.[43] Other laboratories have reported clinical and histologic remission after syngeneic HSCT but persistence of myelin reactive T cells post transplant.[45] This would suggest that the mechanism of clinical tolerance might be through a cytokine shift, enhancement of regulatory cells, or inability of T cells to home to the central nervous system (CNS).

Due to the expense of long term animal housing, most EAE experiments are performed prior to disease onset in order to abort disease initiation or shortly after disease onset in order to ameliorate its course. It is unlikely that such experiments are applicable to patients with a long duration of MS with

accumulated disease burden and tissue damage. Syngeneic HSCT performed in mice with chronic EAE, unlike the results in acute EAE, failed to demonstrate neurologic improvement.[45] Histologic analysis revealed chronic scarring with glial proliferation that is unaffected by HSCT.[45] To be effective as therapy for EAE, it is hypothesized that HSCT needs to be performed early in disease course during its inflammatory stage and before accumulation of disease burden.

Murine bone marrow transplants are performed by euthanizing and removing the femur from the donor and using a syringe to flush out the marrow cells. It is technically difficult and inhumane to perform a murine autologous transplant since the surviving recipient's legs would have to be amputated. However, marrow could be harvested from a syngeneic donor in the same active stage of EAE as the recipient; this is referred to as a pseudo autologous transplant. HSCT of EAE using pseudo autologous donors suggests that infused lymphocytes contaminating the graft may contribute to relapse.[46] This indicates that lymphocyte depletion of grafts may be important in decreasing post transplant relapse following autologous HSCT.
Several other environmentally induced animal autoimmune diseases are improved or cured by syngeneic or autologous HSCT. These include experimental autoimmune myasthenia gravis[52] and adjuvant- and collagen-induced arthritis.[42,44] In a mouse model of lupus-like autoimmunity accompanied by coronary artery disease (associated with antibodies to phospholipid), transplantation of syngeneic stem cells depleted of T cells prevents disease.[53] Nephritis can also be prevented in BXSB lupus mice with establishment of mixed chimerism using bone marrow cells.[54] However, murine models of lupus are stem cell defects that require an allogeneic transplant to be cured.

A spontaneous lupus-like illness occurs in many species including dogs, monkeys, and mice. Most studies have, for economical reasons, been confined to highly inbred murine strains.[55] New Zealand Black (NZB) mice develop a spontaneous hemolytic anemia. When NZB mice are mated to normal New Zealand White (NZW) mice the F1 offspring (NZB x NZW) or B/W mice develop antinuclear antibodies (ANA), anti-ds DNA antibodies, and early death from glomerulonephritis.[56] Disease occurs in both males and females but is more severe in females. The B/W lupus-like illness arises from polygenic loci contributed by both parents. At least 8 genes on multiple chromosomes are involved and may be inherited in a dominant or recessive manner.[57] Individual loci appear to be linked to different stages of disease (e.g. antibody formation, glomerulonephritis, or mortality). Mating NZB mice to another normal mouse strain (SWR) also results in offspring (SNF1) with a lupus-like illness. SNF1 mice have disease similar to B/W mice manifest by spontaneous onset autoantibodies, glomerulonephritis, female predominance, and linkage to polygenic loci.[58]

The Murthy Roth lab lymphoproliferative (MRL/lpr) mouse develops massive lymphadenopathy, glomerulonephritis, erosive arthritis, polyarteritis, hypocomplementemia, and a variety of autoantibodies including: ANA, anti-ds DNA, anti-Sm, rheumatoid factor, and anti-phospholipid antibodies.[59] The congenic MRL/+/+ mouse develops similar serologic abnormalities and glomerulonephritis but does not develop lymphoproliferation and disease is milder with a life span of up to 24 months. In contrast, MRL/lpr mice die within 3-6 months. As mentioned, MRL/lpr and MRL/+/+ mice are congenic which means that they have been bred for consecutive generations to differ in only one loci. This single loci difference, the lpr gene, encodes a defective Fas molecule.[60] Surface Fas expression, when engaged by the Fas ligand, induces apoptosis. Therefore, a single gene defect, Fas, results in an accelerated autoimmune phenotype in a genetically susceptible strain.

The BXSB strain of mice also develops a spontaneous lupus-like illness.[61] The disease is worse in males than females. Acceleration of disease phenotype in males is due to a Y chromosome gene termed Y chromosome autoimmune accelerator (*Yaa*).[62] The function of the *Yaa* gene is unknown but unless expressed in a susceptible strain is unable to cause disease. *Yaa* has been postulated to increase expression of adhesion molecules aiding T cell stimulation of B cells. Finally, male offspring of BXSB x NZW mice develop antibodies to DNA, platelets and phospholipids and die of accelerated coronary artery disease.[63] This is pertinent to lupus patients since some suffer from increased vascular events including coronary artery disease.

Immune cells arise from the hematopoietic compartment. Therefore, hematopoietic (i.e. bone marrow) transplantation from a non-disease susceptible donor has been attempted to treat animal autoimmune disease.[64-67] Allogeneic bone marrow transplantation (i.e. immune ablation and infusion of hematopoietic stem cells from a normal strain) prevents and/or cures lupus-like disease in BXSB and B/W mice.[64,65] While allogeneic HSCT can cure lupus-like disease, it is generally thought that autologous or syngeneic marrow transplantation would transplant disease prone cells and be ineffective. Although not curative, lymphocyte depleted syngeneic marrow transplantation induces life-prolonging remissions in MRL/lpr mice.[66, 67]

Application of these murine lupus-like models to SLE must be done with caution since the mice originate from highly inbred strains. Murine models are important to identify genetic loci mediating autoimmune phenomena. However, in outbred human populations, environmental exposure and regulatory cells and other suppressor mechanisms may have significant roles in controlling disease-associated genes. In fact, unlike murine models of lupus, patients with SLE can enter spontaneous remissions off therapy. Therefore, the potential for autologous HSCT to cure SLE remains possible but uncertain.

1.5.2. Preliminary clinical experience with hematopoietic stem cell transplantation

Anecdotal case reports of patients with a coincidental autoimmune disease and a malignancy provide further support and rationale for trial design.[68-78] Refractory autoimmune diseases enter remission sometimes for several years. In these anecdotal reports, the indication for transplant was a malignancy or aplastic anemia and the outcome reported retrospectively, and therefore in most cases a detailed pre transplant evaluation by a rheumatologist or neurologist is missing. The results in these cases are that the autografts were usually not purged of lymphocytes, and the transplants were not tailored as therapy for an autoimmune disease. Duration of response appeared shorter for rheumatoid arthritis compared to systemic lupus erythematosus. Too few patients have been reported for other autoimmune diseases and long-term results of response to treatment in those that relapse as well as duration of remission in those that had not relapsed remains unknown.

Autologous transplantation performed for malignant disease is associated with a prolonged, post transplant "immunosuppressive" phenotype, which has recently been reported by our group to exist after autologous transplantation of autoimmune diseases as well.[79] This generalized "suppresser" phenotype is manifest by a low CD4 count, elevated CD8 percentage, an inverted CD4/CD8 ratio, and an early predominance of CD45RO memory cells followed after 3-6 months by recurrence of CD45RA naive cells. There is speculation that high dose immunosuppression, by inducing apoptosis of disease causing lymphocytes and imposing a post transplant suppresser phenotype, may be beneficial in inducing a sustained remission of lupus. We, therefore, chose the safer autologous stem cells over an allogeneic source of stem cells for the phase I study.

1.5.3. Phase I study at Northwestern University

A phase I study to perform lymphocyte depleted autologous hematopoietic stem cell transplantation for patients with poor prognosis systemic lupus erythematosus was initiated in 1996 following U.S. FDA approval. Thirty-one patients have undergone transplant. We reported the first patient as a letter to the *New England Journal of Medicine*[80] and subsequently reported further results as articles in *The Lancet*[35] and *Arthritis and Rheumatism*[36]. The reasoning that went into the development of that protocol is recounted here as it is relevant to our current proposal. Cyclophosphamide was chosen as the immunosuppressive regimen because of its established effectiveness at conventional dosage in the treatment of lupus. All transplant candidates had to have failed monthly pulse cyclophosphamide at 500-1000 mg/m^2. We recognized that the dose limiting toxicity of cyclophosphamide, unlike most

alkylating agents, is not hematopoietic. Even without reinfusion of stem cells, cyclophosphamide-induced cytopenias will resolve. In recognition of this fact, some investigators have performed immunosuppressive trials in autoimmune diseases using high dose cyclophosphamide without stem cell reinfusion. We chose to reinfuse G-CSF mobilized hematopoietic stem cells in order to minimize the duration of cyclophosphamide induced neutropenia. We reasoned that the patients who met our eligibility criteria, having been heavily pretreated with immunosuppressive medications, would be at high risk of opportunistic infection. This proved true. Two patients who met our eligibility criteria could not be taken to transplant because of opportunistic infections (cytomegalovirus pneumonitis and mucormycosis). Both were diagnosed prior to transplantation and after a transient period of neutropenia (ANC < 500/ul for 2-3 days) associated with stem cell mobilization.

Methods

Method of Harvesting Stem Cells: Hematopoietic stem cells were mobilized with cyclophosphamide (2 g/m^2) and G-CSF. Engraftment kinetics is faster with G-CSF mobilized peripheral blood stem cells compared to marrow. Due to the anticipated high risk of infection in patients with SLE, we felt that the rapid engraftment of peripheral blood stem cells would be superior to that of marrow. In fact, most autologous transplants for malignancies now use peripheral blood mobilized stem cells rather than marrow due to more rapid engraftment, less infections, and more rapid hospital discharge. We were concerned that attempts to mobilize peripheral blood stem cells with G-CSF (an inflammatory cytokine) would be dangerous for patients with active SLE. For this reason, cyclophosphamide (2.0 mg/m^2) was given first with G-CSF started 4-5 days later. This dose of cyclophosphamide caused neutropenia of 1-3 days duration. Leukapheresis was initiated when the post nadir white blood cell count reached more than 1,000/ul (1.0 x 10^9/liter). Daily apheresis was continued until the number of harvested progenitor cells reached a minimum of 1.4 x 10^6 CD34$^+$ cells/kg body weight after selection. The mobilized peripheral blood stem cells were lymphocyte depleted via selection for CD34 positive cells using the CEPRATE SC Stem Cell Concentrator (CellPro, Bothell, Washington).

Patient selection: In order to select for patients at high risk for early mortality, we chose patients with active visceral disease despite the use of pulse cyclophosphamide and corticosteroids. Cyclophosphamide must have been given for at least 6 months for patients with nephritis (WHO class III or class IV glomerulonephritis). With other visceral organ involvement, failure to prevent life-threatening manifestations (e.g. cerebritis, transverse myelitis, pulmonary hemorrhage, restrictive lung disease or cardiac failure) between pulses of cyclophosphamide was also an indication.

Conditioning Regimen: On pre-transplantation days –5 to –2, patients were given daily intravenous doses of 50mg/kg cyclophosphamide. On pre-transplantation days –4 to –2, patients were given 250-1000 mg methylprednisolone intravenously, followed by 30 mg/kg antithymocyte globulin.

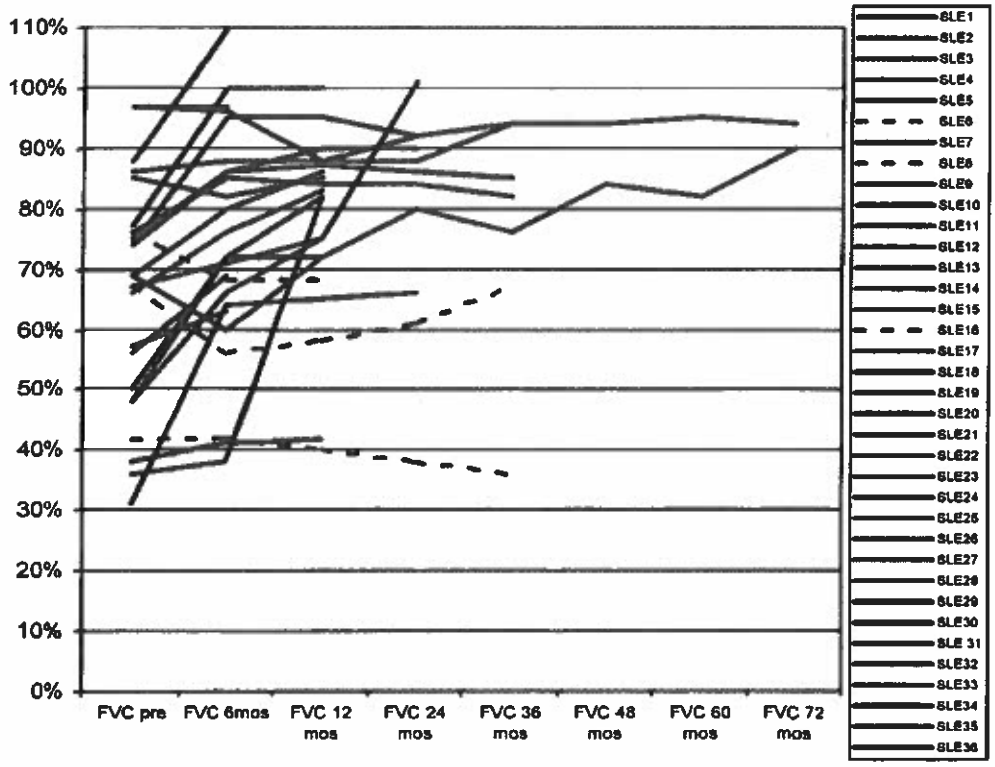
Upon admission to the HEPA-filtered hematology/oncology floor, patients started a low microbial diet which was discontinued when the absolute neutrophil count rebounded to 0.5 x 10^9/L. Additionally, patients began 750 mg oral ciprofloxacin twice daily, which was changed to intravenous piperacillin and tazobactam plus liposomal amphotericin B 3.0-5.0 mg/kg/day when the absolute neutrophil count fell below 0.5 x 10^9/L.

Beginning on the day of hematopoietic stem cell infusion, patients were given subcutaneous granulocyte colony stimulating factor 5 mcg/kg until the absolute neutrophil count was greater than 1.0 x 10^9/L. For 6 months following transplantation, patients were treated with daily valtrex; fluconazole, voriconazole or itracanozole; and monthly aerosolized pentamidine.

Results

Patients transplanted: A total of thirty-one patients, ages 15-53 years, with SLE have undergone transplant. The initial outcomes have been reported in both the *New England Journal of Medicine* and *The Lancet*. A report of all 32 patients is in preparation. All were corticosteroid dependent with daily prednisone dose ranging from 60 to 100 mg per day. All had failed between 8 to 18 monthly cycles of IV cyclophosphamide except for patient 2 in whom three cycles of IV cyclophosphamide and plasmapheresis failed to control pulmonary hemorrhage. Post transplant follow-up ranges from 2 to 60 months with a median of 28 months. No patient who underwent HSCT has died. Marked improvement has occurred in organ function for all patients despite gradual withdrawal of all immune suppression. An example of pulmonary improvement post HSCT in all 32 patients follows below.

DLCO BEFORE AND AFTER HSCT IN 32 SLE PATIENTS UNDERGOING HSCT AT NORTHWESTERN



1.5.4. Phase I Study Worldwide

Hematopoietic stem cell transplants for SLE have also been ongoing in Europe. A summary of the European case reports follows in Table 2. These reports have been equally encouraging with remissions up to 3 years.

Table 2: Published Results on HSCT for SLE in Europe

Disease reference	Conditioning regimen	Number of patients	Result
SLE (81)	Thiotepa, cyclophosphamide	1	Remission for >3 years
SLE (82)	Cytoclophosphamide ATG	2	Remission for > 12 months
SLE (79)	BEAM	1	Remission for >1 year
SLE (83)	Cyclophosphamide, ATG	1	Remission for 8 months

2. Study Rationale

2.1. Selection of Study Population

The phase I study discussed in Section 1.6.3 was designed to select patients with refractory and intractable disease. While those study results were promising, HSCT of patients with impaired visceral organ function and chronic exposure to glucocorticoid therapy is a complicated and high-risk procedure. Enrolling participants earlier in disease who are less ill would also decrease the morbidity and mortality of HSCT. For this reason, the entry criterion for visceral but non-renal involvement is lessened for the current study. Participants with extra-renal lupus need to fail 3 months (instead of 6 months) of monthly cyclophosphamide. For participants in whom the indication is nephritis, active disease must be present despite at least 6 cycles of monthly pulse cyclophosphamide.

2.2. Summary of the Known and Potential Risks and Benefits to Human Subjects

2.2.1. Risks

Participation in this trial is associated with certain risks both from the high dose therapy and from the stem cell transplantation.

Cyclophosphamide. The administration of high dose cyclophosphamide is associated with risk of myelosuppression, leukopenia (nadir 8-14 days), hemorrhagic cystitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), bladder carcinoma, cellular dysplasias, mucositis, rash, alopecia, anorexia, nausea, vomiting, sterile phlebitis, rare pulmonary toxicity, teratogenicity, hemorrhagic myocarditis, infertility, secondary leukemia; and with rapid IV push oropharyngeal tingling, metallic taste, headache, urticaria, and facial swelling.

Hematopoietic stem cell transplantation: The major hazard of this protocol is transplant-related morbidity and mortality. The marrow suppressive regimen of cyclophosphamide and anti-thymocyte globulin will temporarily destroy the hematopoietic ability of the patient's marrow, and leave the patient susceptible to a wide variety of infections and bleeding complications until the re-infused marrow engrafts. Aggressive supportive care as described above will be used to prevent all avoidable risk. However, a small percentage of participants (expected to be less than 5%, based on previous autologous BMT reported studies) may die as a direct result of transplant related complications. Transplant related mortality is directly related to a participant's age, general medical condition, organ dysfunction, and prior exposure to prolonged or aggressive chemotherapy regimens. Transplant related complications include infections, bleeding, veno-occlusive disease of the liver, and failure to engraft.

Risk from rabbit ATG/rituximab: "serum sickness" (a hypersensitivity reaction consisting of fever, rashes, joint pain and kidney disease); anaphylaxis

(sudden and severe allergic reaction that could result in death); chills, pains in your joints, headache, muscle pain, nausea, vomiting, diarrhea, chest-pain, low blood pressure, shortness of breath, fluid in the lungs, abdominal pain; abnormal liver function and renal function; and low blood platelet count. Low CD4+ counts may also occur and may result in death related to infection.

Risk from G-CSF: myalgias, headache, flu-like symptoms, fever, bone pain in approximately 20% of participants, possible elevation of uric acid, transaminases, and LDH.

Risk from Leukapheresis: This procedure requires 4-6 hours and will be performed through the pheresis catheter or a 16-gauge catheter introduced into the antecubital vein. The total volume outside the body at any time does not exceed 450 ml. The most common complication is hypocalcemia arising from citrate anticoagulation, which is usually mild or rarely severe with nausea, vomiting or arrhythmias. Symptoms are avoided with replacement solutions added during apheresis, slowing the flow rate, and/or supplemental oral antacids containing calcium. Other complications are infrequent, but include hypotension, vasovagal syncope and infection.

Central Line: Placement of an external central line catheter device is a routine procedure, which may be done under local or general anesthesia. Potential complications include bleeding, pneumothorax, hemothorax, or arrhythmia. Like all artificial devices, lines may become infected and require treatment with antibiotics and/or removal.

2.2.2. Benefits

If the phase I results can be replicated, participants who receive SCT should benefit with corticosteroid-free remissions for three or more years. This is in contrast to participants who receive treatment with cyclophosphamide, many of whom will continue to have active disease requiring treatment.

3. Objectives

This trial is designed to evaluate the safety of treating systemic lupus erythematosus participants with high dose cyclophosphamide and rATG/rituximab immune ablation, followed by rescue with unmanipulated peripheral stem cells.

4. Endpoints and Outcomes

4.1. Primary Outcome

The primary efficacy outcome is overall survival and the proportion of participants who achieve and maintain remission after transplant. Remission is defined according to the RIFLE as duration on no immune suppressive medications except physiologic doses of prednisone (<10 mg/day) or corticosteroid equivalent and or hydroxychloroquine

4.2. Secondary Outcomes

The secondary efficacy outcomes include the following:

1) Serology, ANA titer, anti-ds DNA antibody titer, and C3 and C4
2) SLEDAI
3) CrCl and DLCO Adj

5. Study Design and Populations

5.1 Study Population

Participants meeting the inclusion and exclusion criteria specified below may be enrolled.

5.1.1. Inclusion Criteria

The inclusion criteria are:

- Ages 15 to 60 years old
- Meet at least 4 of 11 American College of Rheumatology (ACR) Classification criteria for SLE (see Appendix 16.2)
- Meet one of following five:
    a) For lupus nephritis, participants must fail pulse cyclophosphamide (500 to 1000 mg/m^2 monthly for a minimum of 6 months) or cell cept. Failure is defined as meeting criteria to be considered as BILAG renal category A.
    b) For visceral organ involvement other than nephritis, participants must be BILAG cardiovascular/respiratory category A, vasculitis category A, or neurologic category A and must fail at least 3 months of oral or IV cyclophosphamide and be corticosteroid dependent. Steroid dependence being defined as at least 3 months of steroid therapy and inability to wean corticosteroid to less than 20 mg/day of prednisone or equivalent.

c) For cytopenias that are immune mediated, participants must be BILAG hematologic category A. Participants must fail corticosteroids (either oral prednisone > 0.5 mg/kg/day for more than 6 months or pulse methylprednisolone for at least one cycle of three days), and at least one of the following: azathioprine at 2 mg/kg/day for at least 3 months, mycophenolate mofetil 2 grams daily for more than 3 months, cyclophosphamide intravenously or orally for at least 3 months, or cyclosporine at least 3 mg/kg/day for at least 3 months, danazol for at least 3 months, or splenectomy.

d) For mucocutaneous disease, participants must meet BILAG mucocutaneous category A, be unable to be weaned from prednisone to less than 0.5 mg/kg/day for more than 6 months and obvious Cushingoid habitus, and have received at least one of the following: azathioprine at 2 mg/kg/day for at least 3 months, methotrexate at 15mg/week for at least 3 months, cyclophosphamide intravenously or orally for at least 3 months, or cyclosporine at least 3 mg/kg/day for at least 3 months.

e) For arthritis/myositis, participants must meet BILAG musculoskeletal category A, be unable to be weaned from prednisone to less than 0.5 mg/kg/day for more than 6 months and obvious Cushingoid habitus, and have received at least one of the following: azathioprine at 2 mg/kg/day for at least 3 months, methotrexate at 15mg/ week for at least 3 months, cyclophosphamide intravenously or orally for at least 3 months, or cyclosporine at least 3 mg/kg/day for at least 3 months.

- Able to give informed consent.
- If indication for HSCT is nephritis, a renal biopsy must demonstrate the potential of a reversible (non-fibrotic) component indicating that if successful the participant would not be likely to be permanently dialysis-dependent after transplant.
- Since the BILAG is only one of multiple indices for SLE, patients may also be candidates if despite prior immune suppression therapy as described above, patients are still on active immune suppression (more than 10mg a day of prednisone).
- Patients with SLE whose major manifestation is Antiphospholipid syndrome (APS) may be candidates without prior immune suppression therapy if they have had a visceral organ thrombotic or embolic event despite anticoagulation.

5.1.2. Exclusion Criteria

- HIV positive
- Ongoing malignancy except localized basal cell or squamous skin cancer. Other malignancies for which the participant is judged to be cured by local surgical therapy, such as head and neck cancer, or stage I or II breast

cancer will be considered on an individual basis by the investigators doing the final screening for participant qualification.

- Positive pregnancy test, inability or unwillingness to pursue effective means of birth control, failure to willingly accept or comprehend irreversible sterility as a side effect of therapy.
- Psychiatric illness or mental deficiency making compliance with treatment or informed consent impossible.
- DLCO < 45% of predicted unless attributed to active lupus.
- Resting LVEF < 40% unless attributed to active lupus.
- Known hypersensitivity to E Coli derived proteins.
- Transaminases greater than 2 times normal unless attributed to active lupus.
- Positive tuberculosis skin test
- Any active infection
- Any co-morbid illness that in the opinion of the investigator would jeopardize the ability of the subject to tolerate the study.
- Failure to collect at least 2.0 x 10^6 CD34+ cells/kg
- ANA-negative

6. Study Treatment and Concomitant Therapies

6.1. Preparation, Administration and Dosage of Study Treatment

6.1.1. Mobilization

Participants will be administered Cyclophosphamide at 2.0 g/m^2 in 200 ml of normal saline (NS) over 1 hour. Hydration with 0.9 NS at approximately 100-250-ml/ hour will begin 4 hours prior to cyclophosphamide and continued for 24 hours after termination of cyclophosphamide. Urine output approximately greater than 100 ml/hour should be maintained.

G-CSF will be administered subcutaneously at 5-10 mcg/kg/day and will be started 5 days after termination of cyclophosphamide administration.

After the absolute neutrophil count is greater than 1000/ul or after hematological nadir, leukapheresis using a continuous flow blood cell separator will be initiated. A 10-15 liter apheresis will be performed unless stopped earlier for clinical judgment of toxicity (e.g., numbness, tetany). The G-CSF will continue until apheresis is discontinued. If necessary, platelets will be transfused to greater than 60,000/ul prior to each apheresis.

Table 3: Stem Cell Mobilization with Cyclophosphamide and G-CSF

DAY	0	1	2	3	4	5	10 +	ANC >1.0
Cyclophosphamide 2 gm/m^2	X							
G-CSF (5-10 mcg/kg/day)				X	X	X	X	X
Apheresis*								X

* Apheresis begins when ANC > 1.0 x 10^9/L and continues until >2.0 x 10^6 CD34 cells/kg patient weight are cryopreserved. A maximum of 4 apheresis may be performed. If the minimum number of CD34 cells (2.0 x 10^6 /kg) have not been collected, the patient will not receive the conditioning regimen or HSCT.

6.1.2. Conditioning Regimen

Table 4. Conditioning Regimen

Day	-6	-5	-4	-3	-2	-1	0	+1	+6
Hydration	X	X	X	X	X				
Cyclophosphamide (50 mg/kg/d)		X	X	X	X				
Mesna		X	X	X	X				
Rabbit ATG (mg/kg/d) IV		0.5	1	1.5	1.5	1.5			
Solumedrol 250 mg IV		X	X	X	X	X			
Rituximab 500mg/d IV	X							X	
Stem Cells infused							X		
G-CSF 5mcg/kg/d start D+6									X

Hydration: approximately 50-200cc/hour in adults should begin 6 hours before cyclophosphamide and continue until 24 hours after the last cyclophosphamide dose. Hydration rates need to be individually adjusted by daily weights to maintain dry weight count. BID weights will be obtained. **Warning:** Participants with renal insufficiency are prone to volume overload. Early institution of ultrafiltration or dialysis is recommended.

Cyclophosphamide: 50 mg/kg/day x 4 days (the lesser of ideal or actual weight) will be given intravenously over 1 hour in 250 cc of normal saline on days -5 through -2.

Mesna: 50mg/kg/day x 4 days will be given intravenously over 24 hours.

Rabbit ATG 0.5mg/kg will be given IV on day –5, 1.0mg/kg will be given on day –4, 1.5mg/kg will be given IV on days –3, -2, -1 (no dose adjustment). It will be given over 10 hours. Premedicate with Solumedrol 250mg IV, acetaminophen 650mg po qd and diphenhydramine 25mg 30 minutes before infusion.

Rituximab 500mg/day will be given IV on days –6 and +1. At the first dose (D-6), rituximab infusion will be started at 50mg/h and escalate the infusion rate by 50mg every 30minutes to a maximum of 400mg/h. Starting the second dose (days –4, -2 and +1). IV infusion will be started at 100mg/h and escalate the infusion rate 100mg every 30minutes to a maximum of 400mg/h. Premedicate with Solumedrol 250mg IV, acetaminophen 650mg po qd and diphenhydramine 25mg 30 minutes before infusion on days –6 and +1. Premedicate acetaminophen 650mg po qd and diphenhydramine 25mg 30 minutes before infusion on days –4 and –2.

G-CSF will be continued until absolute neutrophil count reaches at least 1,000cells/ml for three days

6.1.3. Stem Cell Reinfusion

Previously collected stem cells will be reinfused on day 0 as noted in Table 4. The stem cells are infused over approximately 20 minutes through the central venous catheter (e.g., PICC line). Following stem cell reinfusion, routine daily labs will be obtained including CBC, chemistry panel, and liver function tests. Antibiotics and blood transfusions will be administered as required by clinical judgment.

6.1.4. Infection Prophylaxis Guidelines

All prophylactic antibiotics may be changed or discontinued according to clinical circumstances (such as patient allergy) as determined by attending physician(s).

Antibacterial prophylaxis - Ciprofloxacin 500 mg po BID from day -10 until neutrophil count is less than 500/ul. When ANC is < 500/ul, a broad-spectrum intravenous antibiotic such as Zosyn or Cefepime is recommended regardless of temperature until ANC returns to > 500/ul. Aerosolized pentamidine 300mg will be given monthly for 6 months (bacterial and pneumocystis prophylaxis).

Antifungal prophylaxis – Either Voriconazole 200 mg bid or Ambisome 5mg/kg will be given while neutropenic during both mobilization and transplantation. When

ANC is > 500/ul, Voriconazole is recommended for a minimum of 6 months or longer until the participant is tapered off corticosteroids.

Antiviral prophylaxis – Valtrex 500 mg po TID from day of admission until ANC > 500/ul. Oral valganciclovir (dose adjusted for Cr, WBC and platelets) will be given until day 90. Thereafter, Valtrex is recommended for a minimum of one year or longer until the participant is tapered off corticosteroids.

6.1.5. Transfusion Guidelines

Since SLE may have a vasculitis component, the platelet count should be maintained over 30,000/ul throughout the transplant period.

6.2. Modification and Discontinuation of Study Treatment or Study Protocol Procedures

All prophylactic antibiotics indicated in Section 6.1.2 may be changed or discontinued according to clinical circumstances (such as patient allergy) as determined by attending physician(s).

The investigator must apply his/her clinical judgment to determine if an adverse event is of sufficient severity to require that the subject should immediately be removed from treatment. If necessary, an investigator must suspend any trial treatments and institute the necessary medical therapy to protect a subject from any immediate dangers.

7.0 Study Parameters—all pre-transplant tests must be obtained within 3 months of study entry

Test / evaluation	Pre-enrollment	Upon admission for HSCT	During hospitalization	Weekly for 4 weeks after transplant	6 mo, 12 mo, then yearly for 5 years*
History and physical	X	X	DAILY SOAP	X	X
Medications /dose	X	X	X	X	X
SLEDAI	X				X
CXR, EKG	X				X (if clinically indicated)
CBC with diff	X	X	X daily	X	X
Electrolytes and Cr	X	X	X daily	X	X
AST, ALT, bili, alk phos	X	X	X three times a week	X	X
Dobutamine stress Doppler echocardiography	X				X (dobutamine optional)
ANA, anti-ds DNA, Anti-SSA, SSB, anti-Sm	X				X
ACLA IGG, IGM, Anti-beta-2 glycoprotein, LA	X				X
C3, C4	X				X
PT, PTT	X				
Hepatitis A, B, C, HTLV-I, HTVL-III, CMV titer	X				
UA, 24 hour urine CrCl and protein	X				X(if clinically indicated)
PFT with DLCO	X				X
HRCT	X (only if clinically indicated)				X (only if clinically indicated)
Marrow biopsy and aspirate (as indicated for patients with cytopenias	X				X (only if clinically indicated)
Pregnancy test	X	X			
Dental consultation	X				
CT scan of sinuses	X (optional)				
Neurocognitive	X (only if indicated for active cerebritis)				X (only if indicated for active cerebritis)
MRI with gad and/or MRA of brain	X (if indicated for active cerebritis)				X (only if clinically indicated)
Quality of life scale (SF-36)	X				X

* EVERY EFFORT WILL BE MADE TO HAVE THE PATIENT RETURN FOR FOLLOW-UP. HOWEVER, IF PATIENT CANNOT RETURN FOR FOLLOW-UP, STUDY TESTS AND MEDICAL EVALUATION WILL BE COLLECTED FROM LOCAL PHYSICIAN AS WELL AS TELEPHONE HISTORY BY STUDY PHYSICIAN AND PROTOCOL NURSE.

7.1 HOSPITAL DISCHARGE GUIDELINES

1) Afebrile with no evidence of active infection
2) Transfusion independent or requiring less than one platelet and or PRBC transfusion per week
3) Adequate oral nutrition
4) Complies with outpatient follow-up schedule, visiting nurse (if required), and labs

8.0 EVALUATION OF TOXICITY

Assessment will be made with regards to toxicity by one of the protocol investigators. Common Toxicity Criteria Scale (see appendix) will be used to grade all non-hematologic toxicities.

9.0 ADVERSE EVENT REPORTING

The Toxicity grading for adverse events is according to NCI common toxicity criteria for adverse events (CTCAE) version 2.0 at website http:/ctep.info.nih.gov (besides being located on the website, CTC v2.0 providing an alphabetical listing of Adverse Events with associated descriptions to grade severity is attached at end of the protocol)

9.1 To be reported by phone (312-695-4960) or FAX (312-695-4961) to Richard Burt:

a) All life-threatening or lethal (Grade 4 and 5) (except grade 4 myelosuppression which is anticipated) reactions. This information is to be immediately reported to Dr Richard Burt who will report it within 72 hours of a working day to the IRB and FDA.

9.2 To be reported in writing within 10 working days to Richard K Burt (312-695-4960)

a) Grade 3 reactions. These will be reported by Dr. Burt on annual reports to the FDA.

10.0 Follow-up procedures for withdrawal subjects

Unless the patient refuses, subjects who withdraw from the study will be followed in a manner consistent with the monitoring plan.

11.0 Statistical Considerations

This is a phase II study of 40 patients. Statistical considerations and safety rules for the protocol are as follows:

11.1 **Stopping rules for transplant-related regimen-related toxicity.** Regimen-related toxicity within the first 28 days after transplant will be determined as follows: non-hematological grade 4 toxicity that fails to resolve in 10 days; and hematological grade 4 toxicity that fails to resolve in 28 days. Operationally sufficient evidence of any ratio of regimen-related toxicity will occur when any of the following ratios is observed: any 2/6 or 4/10, or 6/40.

11.2 **Stopping rules for transplant-related mortality (TRM).** TRM will be defined as death within the first 100 days of transplant due to transplant-related complications. Operationally, this will occur with any 2 of 10 deaths, or 4/40.

11.3 **Any death within the first 100 days will result in halting the study until reviewed and the IRB and FDA notified.**

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13.0 Appendices

13.1 American College of Rheumatology SLE Classification Criteria

The 1982 revised criteria for classification of systemic lupus erythematosus

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *OR* b) Pericarditis--documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or grater than 3+ if quantitation not performed *OR* b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR* b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a) Hemolytic anemia--with reticulocytosis *OR* b) Leukopenia--less than 4,000/mm<>3<> total on 2 or more occasions *OR* c) Lymphopenia--less than 1,500/mm<>3<> on 2 or more occasions *OR* d) Thrombocytopenia--less than 100,000/mm<>3<> in the absence of offending drugs
10. Immunologic disorder	a) Positive LE cell preparation *OR*

	b) Anti-DNA: antibody to native DNA in abnormal titer *OR* c) Anti-Sm: presence of antibody to Sm nuclear antigen *OR* d) False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.
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13.2 Drug Formulations

Cyclophosphamide

Other names:	Cytoxan, Neosar
Description:	2-bis (2-chloroethyl) amino tetrahydro-2H-1, 3, 2-oxazaphosphorine-2-oxide monohydrate
Classification:	Alkylating agent
Action :	Causes prevention of cell division by forming adducts with DNA
Metabolism:	Metabolized to active compounds by microsomal enzymes in the liver. Excreted by the kidney in both the original form and as metabolites.
Availability:	25 mg and 50 mg tablets (tablets cannot be split); 100 mg, 200 mg, 500 mg, 2000 mg vials Mead Johnson and Adria.
Storage:	Stable at room temperature indefinitely before reconstitution. After reconstitution, stable for 6 days upon refrigeration or for 24 hours at room temperature.
Administration:	Dissolved in 250 cc D5W and administered over 30-60 minutes IV. Must be aggressively hydrated before, during, and for 24 hours after cyclophosphamide. The rate of hydration required may not be tolerated in a patient with lupus nephritis and in this case, bladder irrigation may need to be substituted.
Side effects	Myelosuppression, leukopenia (nadir 8-14 days), hemorrhagic cystitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), bladder carcinoma, cellular dysplasias, mucositis, rash, alopecia, anorexia, nausea, vomiting, sterile phlebitis, rare pulmonary toxicity, teratogeneicity, hemorrhagic, myocarditis, infertility, secondary leukemia; with rapid IV push, oropharyngeal tingling, metallic taste, headache, urticaria, facial swelling. Metabolic abnormalities following cyclophosphamide induced cell lysis can require dialysis in-patients with underlying renal insufficiency.

ATG (rabbit)

Other names:	thymoglobulin
Classification:	Biologic response modifier
Action :	A rabbit polyclonal antibody to lymphocytes against human T-lymphocytes. Exact mechanism of action is unknown.
Availability:	50mg/ml (5 ml ample) vial.
Storage:	Store ampules at 2-8 degrees centigrade.
Administration:	Diluted in 250 NS and infused over 10 hours.

ATG (rabbit)	
Side effects	Side effects of ATG are serum sickness and/or anaphylaxis: chills, arthralgias, headache, myalgias, nausea, vomiting, diarrhea, chest-pain, hypotension, dyspnea, pulmonary edema, abdominal pain. Other side effects include abnormal liver function tests (SGOT, SGPT) abnormal renal function, and thrombocytopenia.
Rituximab	
Other names:	Rituxan®
Classification:	Biologic response modifier
Action :	chimeric murine/human monoclonal antibody to the CD20 molecule on B-lymphocytes, The molecule is combined with Fc fragment of human IgG 1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequence and human constant region sequences. Exact mechanism of action is unknown.
Availability:	10mg/ml (10 ml and 50ml amples).
Storage:	protected from light at 2-8 degrees centigrade.
Administration:	Patients should be premedicated with 25mg diphenhydramine and 650mg of acetaminophen 30 minutes prior to the each rituximab infusion. The dose of 500 mg will be diluted in 500 cc 0.9%NS and infused per standard rituximab infusion guidelines (start at 50mg/h. If no reaction occurs, increase by 50mg/h every 30 minutes, to a maximum of 400mg/h.
Side effects	The most serious adverse reactions caused by rituximab include infusion reactions, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias and angina, and renal failure. The infusion reactions can be treated with slowing or interruption of the infusion and supportive care (diphenhydramine, acetaminophen, IV saline or vasopressors). Other reactions include: nausea/vomiting/diarrhea, headache, myalgias, arthralgias, cough, rhinitis, broncospasm, dyspnea, sinusitis, lymphopenia, leukopenia, neutropenia, thrombocytopenia, anemia, abdominal pain, back pain, throat irritation, asthenia, infection. Reactivation of hepatitis B virus and progression to fulminant hepatitis has been reported in patients with negative hepatitis B surface antigen, but positive hepatitis B surface antibody.
G-CSF	
Other names:	Filgrastim, Neupogen
Classification:	Colony stimulating factor

G-CSF

Action :	Stimulates the production, maturation, and activation of neutrophils, G-CSF activates neutrophils to increase both their migration and cytotoxicity.
Availability:	300 mcg and 480 mcg vials
Storage:	Stored in refrigerator
Administration:	Subcutaneous administration 5-15 mcg/kg/day
Side effects	Myalgias, headache, flu-like symptoms, fever, Bone pain in approximately 20% of patients, possible elevation of uric acid, transaminases, and LDH.

13.2 SF-36

Short Form- 36 Health Survey (SF-36)

INSTRUCTIONS: The survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. **In general, would you say your health is:** (circle one)

   Excellent 1

   Very Good 2

   Good 3

   Fair 4

   Poor 5

2. **COMPARED TO ONE YEAR AGO, how would you rate your health in general NOW:** (circle one)

   Much better now than one year ago 1

   Somewhat better now than one year ago 2

   About the same as one year ago 3

   Somewhat worse now than one year ago 4

   Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

ACTIVITIES	Circle one number on each item Yes, Limited A Lot	Yes, Limited A Little	No Not Limited At All
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
b. Moderate activities, such as moving a table pushing a vacuum cleaner, bowling, or playing golf.	1	2	3
c. Lifting or carrying groceries.	1	2	3
d. Climbing several flights of stairs.	1	2	3
e. Climbing one flight of stairs.	1	2	3
f. Bending, kneeling, or stooping.	1	2	3
g. Walking more than a mile.	1	2	3
h. Walking several blocks.	1	2	3
i. Walking one block.	1	2	3
j. Bathing or dressing yourself.	1	2	3

4. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

Circle one number on each line

		YES	NO
a.	Cut down on the amount of time you spent on work or other activities.	1	2
b.	Accomplished less than you would like.	1	2
c.	Were limited in the kind of work or other activities.	1	2
d.	Had difficulty performing the work or other activities (for example, it took extra effort).	1	2

5. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?** Circle one number on each line.

		YES	NO
a.	Cut down on the amount of time you spent on work or other activities.	1	2
b.	Accomplished less than you would like.	1	2
c.	Don't do work or other activities as carefully as usual.	1	2

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Circle one

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. **How much bodily pain have you had during the past 4 weeks?**

Circle one

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very Severe	6

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Circle one

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.**

How much of the time during the past 4weeks --

	All the Time	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None
a. Did you feel full of pep?	1	2	3	4	5	6	
b. Have you been a very nervous person?	1	2	3	4	5	6	
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6	
d. Have you felt calm and peaceful?	1	2	3	4	5	6	
e. Did you have a lot of energy?	1	2	3	4	5	6	
f. Have you felt downhearted and blue?	1	2	3	4	5	6	
g. Did you feel worn out?	1	2	3	4	5	6	
h. Have you been a happy person?	1	2	3	4	5	6	
i. Did you feel tired?	1	2	3	4	5	6	

10. During the *past 4 weeks,* how much of the time has your *physical health or emotional problems* interfered with your social activities (like visiting friends, relatives, etc.)?

Circle one

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

11. How TRUE or FALSE is *each* of the following statements for you?

(Circle one number on each line)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am healthy as anybody I know.	1	2	3	4	5
c. I expect my health to get worse.	1	2	3	4	5
d. My health is excellent.	1	2	3	4	5

Patient's initials: _____ Date: _____

I confirm that the information on this survey is accurate.

Staff initials: _____ Date: _____