Lymphocyte Depletion and Stem Cell Transplantation to Treat Severe Systemic Lupus Erythematosus

This study is currently recruiting patients.

Verified by National Institutes of Health Clinical Center (CC) October 31, 2005

Sponsored by:	National Cancer Institute (NCI)
Information provided by:	National Institutes of Health Clinical Center (CC)
ClinicalTrials.gov Identifier:	NCT00076752

Purpose

This study will examine a new approach to treating patient with severe systemic lupus erythematosus (SLE) that involves collecting stem cells (cells produced by the bone marrow that develop into blood cells) from the patient, completely shutting down the patient's immune system, and then giving back the patient's stem cells. SLE is a chronic, inflammatory disorder of the immune system that can affect many organs. It is called an autoimmune disease because the patient's lymphocytes (white blood cells that normally protect against invading organisms), go out of control and attack the body's own tissues.
Patients between 15 and 40 years of age with severe SLE affecting a major organ that is resistant to standard treatment may be eligible for this study. Candidates are screened with a medical history and physical examination, blood and urine tests, skin tuberculin test, and radiology studies to evaluate the extent of disease. They have endocrinology, nutrition, dental, and social work consultations, ultrasound or MUGA scan heart imaging, electrocardiogram and lung function tests, bone marrow biopsy, and lymph node aspirate. Depending on which organs are affected, patients may have additional tests, such as lumbar puncture (spinal tap), kidney or lung biopsy, MRI of the brain and spinal cord, and PET scan. They also complete quality of life questionnaires and have disability functional testing and neurocognitive (thinking) assessments.
Participants have a central venous line (plastic tube) inserted into a neck or chest vein for administering stem cells and medicines and for drawing blood. They undergo seven apheresis procedures during the course of the study to collect stem cells for transplant and for research. For apheresis, whole blood is collected through a needle in an arm vein and directed to a cell-separating machine where the white cells are extracted and the rest of the blood is returned to the patient through the same needle.
Patients are primed with three medications (methylprednisolone, rituximab, and cyclophosphamide) through the central line to help control the disease. In addition, a medication called G-CSF is injected under the skin for several days to boost production of stem cells. After enough stem cells have been collected for transplantation (infusion through the central line), patients are admitted to the hospital for

an 8-day conditioning regimen followed by transplantation. The conditioning treatment consists of rituximab, fludarabine, and cyclophosphamide to eliminate all the white blood cells from the blood and bone marrow. The stem cells are then infused and the patient is closely monitored by a team of physicians and nurses. When the stem cells have engrafted, the bone marrow has recovered, and the patient feels well enough - usually 2 to 3 weeks after transplant - the patient is discharged from the hospital. Prednisone tapering begins as soon as feasibly possible, but no later then 28 days after transplant.
Patients return to the NIH Clinical Center for frequent follow-up visits during the first 2 to 3 months following transplant. The time between visits is then extended to once every 3 months the first year, then every 6 months the second year, and then at least yearly for 5 years after the transplant. These visits include a physical examination, blood and urine tests, lumbar puncture (if there is central nervous system involvement), other appropriate biopsies and tests as needed to monitor the patient's health, short apheresis procedures to collect blood for research purposes, and quality of life questionnaires. Some select procedures will be optional. Bone marrow biopsies and lymph node aspirates are done at beginning and at 6, 12, and 24 months after transplant. PET scans are done at 1, 6, 12, and 24 months.

Condition	Intervention	Phase
Lupus Erythematosus, Systemic	Drug: Isolex/Rituximab	Phase II

MedlinePlus related topics: Lupus

Study Type: Interventional
Study Design: Treatment, Safety/Efficacy

Official Title: A Pilot Study of Intensified Lymphodepletion Followed by Autologous Hematopoietic Stem Cell Transplantation in Patients with Severe Systemic Lupus Erythematosus

Further study details as provided by National Institutes of Health Clinical Center (CC):

Expected Total Enrollment: 14

Study start: January 29, 2004

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can involve almost any organ and can range in severity from mild to life-threatening. In spite of significant improvements in survival of SLE patients over last 20 years, a small but significant portion of patients still develop progressive, therapy-refractory disease that impairs organ function and overall survival. Since 1996, more than 500 patients have been treated worldwide in pilot trials of autologous hematopoietic stem cell transplantation (autoHSCT) for autoimmune diseases, including about 80 patients with SLE. The rationale for autoHSCT in autoimmune disease is to ablate autoreactive immune effectors and allow reconstitution of a new self-tolerant immune system from the hematopoietic stem cell. Studies have demonstrated acceptable safety and promising short-term efficacy of high-dose cyclophosphamide-based

(200 mg/kg) autoHSCT for about 60% of patients with advanced refractory SLE and reacquisition of sensitivity to conventional drugs has been demonstrated in many cases. However, these trials were designed to address the primary endpoint of safety and were inadequate for assessing the disease-response. Numerous questions about the true efficacy of autoHSCT, optimal transplant regimen, patient selection and mechanisms of action remain unaddressed. The design of this pilot study is based on three guiding principles: first, in order to improve the efficacy of autoHSCT, a lymphoablative conditioning regimen (rituximab, fludarabine and cyclophosphamide) is explored for the first time in autoimmune disease. Second, in contrast to other studies, this study has precisely defined eligibility and disease response criteria with strict schema of tapering immunosuppression that should allow accurate interpretation of the treatment results. Finally, and most importantly, the study includes a carefully chosen battery of laboratory research studies designed to investigate SLE biology and mechanisms of post-transplant responses. Fourteen patients with SLE resistant to standard of care immunosuppression or recalcitrant major organ involvement will be enrolled. The primary objective is to assess the rate of continuous relapse-free complete clinical responses at 24 months post-transplant, with statistical power of 84% to detect, if greater than 70% of patients meet the primary endpoint. The long-term goal of this research is to develop a basis for future transplant protocols that would incorporate new cellular or other immunotherapeutic interventions to further improve results of transplants with the ultimate goal to cure SLE.

Eligibility

Genders Eligible for Study: Both
Criteria
INCLUSION CRITERIA
1. Age 15-40 years
2. Must fulfill at least 4 of the following 11 criteria for SLE as defined by the American College of Rheumatology:
-Malar rash. Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
-Discoid rash. Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
-Photosensitivity. Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.
-Oral ulcers. Oral or nasopharyngeal ulcerations, usually painless, observed by a physician.
-Arthritis. Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion.
-Serositis. a.) Pleuritis - convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion
OR
b.) Pericarditis - documented by ECG or rub or evidence of pericardial effusion
-Renal disorder. a.) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed
OR

b.) Cellular casts - may be red cell, hemoglobin, granular, tubular, or mixed.
-Neurologic disorder. a.) Seizures - in the absence of offending drugs or known metabolic derangements; eg, uremia, ketoacidosis, or electrolyte imbalance
OR
b.) Psychosis - in the absence of offending drugs or known metabolic derangements; eg, uremia, ketoacidosis, or electrolyte imbalance
-Hematologic disorder. a.) Hemolytic anemia - with reticulocytosis
OR
b.) Leukopenia - less than 4000/ L total on two or more occasions
OR
c.) Lymphopenia - less than 1500/ L on two or more occasions
OR
d.) Thrombocytopenia - less than 100,000/ L in the absence of offending drugs
-Immunologic disorder. a.) Anti-DNA: antibody to native DNA in abnormal titer
OR
b.) Anti-SM: presence of antibody to SM nuclear antigen
OR
c.) Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anti-cardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) 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
-Antinuclear antibodies. An abnormal titer of ANAs by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to be associated with drug-induced lupus syndrome.
3. Have severe and active lupus, refractory to immunosuppressive therapy, defined as one of the following (a-d):
a.Nephritis: Biopsy proven Diffuse Proliferative Glomerulonephritis (WHO Class IV) with or without superimposed membranous changes
i.Active disease:
1. A kidney biopsy within three months of enrollment showing active WHO Class IV disease. Activity will be determined based on the presence of endocapillary cellular proliferation compromising the capillary loops or cellular crescents or necrosis on light microscopy or subendothelial deposits on electron microscopy.
2. If a biopsy is contraindicated patients can be enrolled if they had a previous biopsy showing Diffuse Proliferative Glomerulonephritis (WHO Class IV) and at the time of enrollment have all of the following:
a. Proteinuria greater than 1gm/day
b. Active urine sediment defined as hematuria (greater than 10 RBC/hpf on a nephrology urinalysis of a 50 mL urine sample) with dysmorphic RBC and/or cellular casts on a nephrology urinalysis of a 50 mL urine sample
c. Low C3 (less than 69 mg/dL) and/or elevated dsDNA antibodies (greater than 25EU)
3. Need for prednisone greater than 20 mg/day due to increased renal activity after at least 6 months of cyclophosphamide.
ii. Treatment resistant:

1. Patients with active disease after at least 6 months of intravenous pulse cyclophosphamide +/- iv methylprednisolone and daily oral prednisone, or
2. Early flare: those who have reactivation of their nephritis during or within 6 months of completing cyclophosphamide therapy
3. recalcitrant disease: two or more recurrences of lupus nephritis within five years of enrollment. All flares must have received adequate therapy and least one of the episodes must have been treated with minimun 6 months of intravenous pulse cyclophosphamide plus iv methylprednisolone and maintenance oral prednisone.

CNS lupus: Lupus CNS manifestations indicative of encephalitis or myelitis or vasculitis. Concomitant CNS diseases should be excluded. (e.g. infections, multiple sclerosis; patients fulfilling MS and SLE criteria will be excluded). Clinical signs and symptoms must be supported by objective findings of CNS inflammation.

i. Active disease:

Signs/symptoms that are accepted for disease activity:

-Clinical signs and symptoms compatible with focal CNS damage -Severe global neurocognitive/ psychiatric impairment (eg: psychosis, organic brain syndrome, severe depression)

-Intractable seizures

Clinical findings must be supported by at least one of the following:

a) MRI findings consistent with transverse myelitis or
CNS vasculitis

- Signs of inflammation on MRI are either the presence of Gadolinium (Gd)-enhancing lesions, or the increase of the number and/or volume of T2-weighted lesions (or lesions showing up on FLAIR imaging). We will use the standard MS protocol sequences, which are routinely used in the Clinical Center to evaluate inflammatory CNS lesions.

b) If patient has seizures/psychiatric signs and symptoms in the absence of clear signs of vasculitis or cerebritis by MRI, the CSF should show protein elevation above normal levels and abnormal number of WBCs or intrathecal IgG synthesis/or oligoclonal bands.

c) Need for prednisone greater than 20 mg/day due to increased CNS activity (see above) after at least three months of cyclophosphamide therapy.

ii-Treatment resistant:

a) Active disease after a minimum of three months of oral or intravenous cyclophosphamide, or

b) Early flare: reactivation of CNS lupus within 6 months of completing cyclophosphamide therapy

c. Recalctrant disease: two or more recurrences of CNS lupus within five years of enrollment. All flares must have received adequate therapy and at least one of the episodes must have been treated with minimun three months of oral or intravenous cyclophosphamide.

Pulmonary lupus

i. Active disease:

a) Lung biopsy showing active pneumonitis, alveolitis or pulmonary vasculitis after the minimally required therapy within one month of enrollment or

b) If a biopsy is contraindicated within one month of enrollment, patients may be included if they had a biopsy at the start or during cyclophosphamide treatment showing active pneumonitis, alveolitis or pulmonary vasculitis (as above) and have abnormal or worsening pulmonary function tests with a chest CT consistent with active pneumonitis, alveolitis or vasculitis within 2 weeks of enrollment and at the

time of enrollment have a CT consistent with active disease.
c) Need for prednisone greater than 20 mg/day due to increased pulmonary lupus activity after minimum of three months of cyclophophamide.
ii. Treatment resistant:
d) Ongoing or recurrent active pulmonary lupus after a minimum of three months of oral or intravenous cylophosphamide, or
e) Early flare: reactivation of pulmonary lupus (as defined above) within 6 months of completing cyclophosphamide therapy.
f) Recalcitrant disease: two or more recurrences of pulmonary as described above within five years of enrollment. All flares must have received adequate therapy and at least one of the episodes must have been treated with minimum 3 months of oral or intravenous cyclophosphamide.
i) Active disease:
a) Severe immune-mediated thrombocytopenia (platelet count less than 20,000/mm3 or less than 50,000/ mm3 with history of bleeding), or
b) Severe immune-mediated anemia (requiring transfusions to maintain Hb greater than 8.0 g/dL or to treat symptoms of anemia) c) Need for prednisone greater than 20 mg/day due to increased hematologic lupus activity after therapy as described in section ii.a).
ii) Treatment resistant:
a) Active disease as defined above after a minimum of three months of high dose oral or pulse corticosteroids +/- IVIg (or WinRho) and splenectomy, or
b) Early flare: reactivation of hematologic lupus (as defined above) within 6 months of completing above therapy.
c) Recalcitrant disease: two or more recurrences of immune-mediated thrombocytopenia or anemia, as described above, within five years of enrollment. All flares must have received adequate therapy and at least one of the episodes must have been treated by splenectomy.
EXCLUSION CRITERIA
1. Inability to provide written informed consent prior to entry in the protocol
2. Pregnant or lactating women. Women of childbearing potential are required to have a negative pregnancy test at screening
3. Women of childbearing potential who are not practicing or who are unwilling to practice birth control during the entire study
4. Men who are unwilling to practice birth control for the first 6 months after the transplant
5. Evidence of infection with hepatitis B, hepatitis C, or HIV
6. History of malignancy other than basal cell carcinoma of the skin
7. DLCO corrected less than 45%
8. LVEF less than 45%, determined by ECHO cardiogram or MUGA
9. SGOT or SGPT greater than 2x upper limit of normal (unless active myopathy is proven by elevation of serum aldolase levels and the patient has no obvious hepatic disease) and/or bilirubin greater than 2.0 (unless due to isolated hemolysis).
10. Calculated glomerular filtration rate less than 30 ml/min using the MDRD equation estimate: GFR (ml/min/173 m(2)) =186.3 x (Pcr) exponential -1.154 x (age) exponential -0.203 x 1.212 (if black) x 0.742 (if female)
11. Late flare (patients who have target organ flare, that is not within the time frame defined as early

flare, will not be considered as treatment failures until they receive the minimally required therapy for this flare episode and fail to respond to it)
12. Abnormal bone marrow cytogenetics
13. Significant concurrent medical condition or any significant circumstance that could affect the patient's ability to tolerate or complete the study
14. Live vaccines within 4 weeks of starting the priming regimen

Location and Contact Information

Please refer to this study by ClinicalTrials.gov identifier NCT00076752

Maryland

National Cancer Institute (NCI), 9000 Rockville Pike, Bethesda, Maryland, 20892, United States; Recruiting
Patient Recruitment and Public Liaison Office 1-800-411-1222 prpl@mail.cc.nih.gov
TTY 1-866-411-1010

More Information

Detailed Web Page

Publications

Shlomchik MJ, Craft JE, Mamula MJ. From T to B and back again: positive feedback in systemic autoimmune disease. Nat Rev Immunol. 2001 Nov;1(2):147-53. Review.

Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, D'Agostino RB, Kuller LH. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol. 1997 Mar 1;145(5):408-15.

Lipsky PE. Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity. Nat Immunol. 2001 Sep;2(9):764-6. No abstract available.

Study ID Numbers: 040095; 04-C-0095
Last Updated: February 9, 2006
Record first received: February 2, 2004
ClinicalTrials.gov Identifier: NCT00076752
Health Authority: United States: Federal Government

ClinicalTrials.gov processed this record on 2006-03-27