SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

1. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PROTOCOL

A. Clinical Response: Clinical response demonstrates a decrease in progression of disease and evidence of an improved repair process. In addition to physical examinations prior to stem cell graft and 6 months post-procedure, laboratory test results serve as evidence of repair process. Internationally recognized lab tests for monitoring systemic lupus erythematosis (SLE) includes:

- Complete blood count (CBC) with differential
- Serum creatinine
- Complement levels
- Liver function tests
- Creatine kinase assay
- Erythrosedimentation rate (ESR)
- C-reactive Protein (CRP) o Anti-dsDNA
- Antinuclear antibody assay (ANA)
- Urinalysis with microscopy

B. Objective: To provide the patient with a treatment that stimulates his / her immune system, promote cellular regeneration and improve symptoms associated with Systemic Lupus Erythematosus. The endovascular/intravenous Ad-SVF Containing Adult Stem Cell Procedure should serve to compliment the patient's current treatment regimen or to promote healing when current treatment is not responding.

2. PRELIMINARIES

A. Systemic lupus erythematosis (SLE) is a chronic systemic autoimmune disease of unknown cause which follows a relapsing and remitting course. SLE is a multisystem connective tissue disease characterized by the presence of numerous autoantibodies, circulating immune complexes and widespread immunologically determined tissue damage.

B. Treatment Options: Treatment recommendations for SLE depend on disease manifestations and severity of disease. Articular symptoms and less severe inflammatory manifestations should be managed without corticosteroids whenever possible, but NSAIDs must be used with care in patients with renal disease.

- ***Biologic agents***: Monoclonal antibody belimumab (Benlysta), a B-lymphocyte stimulator–specific inhibitor, has been found to reduce disease activity and possibly decrease the number of severe flares and steroid use in patients with SLE, when used in combination with standard therapy. Rituximab (Rituxan) may be used as s rescue therapy for patients with active SLE that is unresponsive to standard immunosuppressant therapy.

- ***Antimalarials***: are particularly useful in the management of patients with troublesome skin and joint lesions and they can reduce the frequency of severe exacerbations of disease.

- ***Aspirin and anticoagulants***: are used to manage patients with anti-phospholipid antibody syndrome

3. AD-SVF CONTAINING ADULT STEM CELLS TREATMENT OPTION

A. Ad-SVF Containing Adult Stem Cells Procedure

- ***Initial patient evaluation***: A physician revises the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

- ***Pre-op Evaluation / post-op medical consultation***: A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment. On the morning prior to procedure history and physical are performed by physician.

- ***Harvesting of adipose tissue***: Adipose tissue acquisition can be summarized as three step process:

    - ***Application of anesthetic / injection of tumescent solution***

    - ***Waiting time***

    - ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. A tissue sample is then obtained using 60 cc syringe(s) to aspirate 50 to 100 cc of adipose tissue. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

- ***Autologous implant of Ad-SVF***: The stem cells obtained from the adipose tissue sample are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused via intravenous infusion in saline.

B. Risks: There are possibilities for unwanted effects related to the local anesthesia, harvesting procedure, and injection of stem cells. Even with the most established protocol, adequate technique, and careful administration; a medical team may encounter uncontrollable events. Although there is no guarantee of perfect results, excellent results can be attained. The surgeon provides services in the most responsible, professional and

diligent manner, always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

- Vascular spasm
- Vascular obstruction
- Pseudo-aneurysms
- Lymphadenopathy
- Swelling of joints
- Pain in joints
- Bruising
- Nerve or muscle injury
- Allergic reaction
- Dizziness
- Nausea / vomiting
- Allergic reaction
- Pain at site of injections
- Bleeding at injection site
- Malaise
- Low-grade fever
- Hot flashes
- Itching at injection site

C. Benefits: Adipose derived stem cells have the potential to repair cartilage and joint tissue. These stem cells also have immune modulating abilities. Adult stem cells possess the ability to repair damaged cells leading to tissue regeneration and ultimately promoting the healing process.

D. Follow-Up Plan: Clinical response demonstrates a decrease of disease activity, decrease in frequency of flare-ups and improvement of symptoms associated with SLE. Review of changes to internationally recognized standards.

- ***Pre-Ad-SVF implant***: Clinical evaluation of SLE symptoms, taking note of any changes in flare-up frequency. Review & record current laboratory results specific to SLE. Follow-up

- ***3 months after Ad-SVF implant***: Clinical evaluation of SLE symptoms, taking note of any changes in flare-up frequency. Review & record current laboratory results specific to SLE.

- ***6 months after Ad-SVF implant***: Clinical evaluation of SLE symptoms, taking note of any changes in flare-up frequency. Review & record current laboratory results specific to SLE.

SLE – Adult Stem Cells Schedule of Events

1. **Initial Patient Evaluation:** A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

   A. Pre-Examination:
   - You will have a physical exam, which will include measuring your blood pressure, temperature and heart rate (vital signs).
   - Your doctor will discuss your medical history and any medications that you are taking.
   - Your doctor will assess how well you can perform your daily activities
   - If needed, you will have a urine or blood pregnancy test.
   - Blood will be taken.

   B. Additional Tests: should be done during or soon after this visit
   - Complete blood count (CBC) with differential
   - Serum creatinine
   - Complement levels
   - Liver function tests
   - Creatine kinase assay
   - Erythrosedimentation rate (ESR)
   - C-reactive Protein (CRP) o Anti-dsDNA
   - Antinuclear antibody assay (ANA)
   - Urinalysis with microscopy

   C. Review Results: After your doctor has reviewed the results of these tests, he or she will assess whether you are a good candidate for stem cell therapy. If you decide to obtain this therapy you will sign a consent form. A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment.

2. **Pre-Operation / Stem Cell Procedure:**

   A. Two Weeks Before Procedure:

   - No Aspirin or medicines that contain aspirin or Ibuprofen since it interferes with normal blood clotting.
   - You may take Tylenol or generic forms of this drug.
   - Discuss with your primary physician to discontinue anticoagulant drugs at least 1 week before the procedure.

- Please discontinue all herbal medications as many have side effects that could complicate a surgical procedure by inhibiting blood clotting, affecting blood pressure, or interfering with anesthetics.
- Please discontinue all diet pills whether prescription, over-the-counter or herbal.
- NO SMOKING because nicotine reduces blood flow to the skin and can cause significant complications during healing.
- Purchase a compressive garment to wear after the lipoaspiration procedure.

B. Morning of the Procedure:

- Have a light breakfast.
- Take your regular prescribed medications
- Wear comfortable, loose-fitting clothes that do not have to be put on over your head.

4. **Stem Cell Procedure:**

A. Preparation & Harvesting of Adipose Tissue:

- ***Application of anesthetic / injection of tumescent solution***
- ***Waiting time (~15 – 20 minutes)***
- ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

B. Autologous implant of Ad-SVF: The stem cells obtained from the adipose tissue sample are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused via intravenous infusion.

1. Recommended Post-Operation / Stem Cell Therapy Schedule:

A. Post-Op Medical Instruction - **(Please follow these instructions closely!)**

- ***Post-op medication*** will be given to you the day of your surgery. They will consist of an antibiotic and a painkiller:
  - *Antibiotic*: Cephalexin/Cipro, please take as directed beginning the day after surgery
  - *Painkiller:* Please take as directed and only as needed for pain

    * If you are unable to take any of these medications, please contact your patient coordinator so we can arrange for other medications.
- ***Resume previous medication*** as directed by the physician
- ***Report any symptoms of feeling unwell***: dizziness, changes in heart rate, pain, or fever. Patients should be seen promptly by an physician for full evaluation should any of the above symptoms be encountered.

- It is recommended that the ***patient have a companion stay with him or her*** for at least 24 hours after discharge.
- You should ***expect some of blood-tinged anesthetic solution to drain from the incision sites*** during the first 24 to 48 hours. This will vary from patient to patient. Maxi-pads are recommended for bandages over your incision sites. You may take a shower 24 hours after the procedure.
- ***Compressive garments should be worn*** 24 hours a day for the first week and 12 hours a day for the second week.
- ***Do not shower for the first 24 hours***. ***Do not submerge yourself in any water*** (i.e. taking a bath or swimming) for the 1st week.
- ***If you experience nausea or vomiting it is probably due to the medication***. Please try to take it with food. If it persists, please contact our office.
- ***Diet-meals are not restricted.***
- ***Drink plenty of clear fluids***. We recommend 8 glasses of water or fruit juice every day.
- ***Do not drink any alcohol*** for 48 hours and limit alcohol intake for the first week.

B. Post-Op Medical Consultation Schedule: 1 month, 3 months, 6 months & 2 years

- ***3 months after Ad-SVF implant***: Clinical evaluation of SLE symptoms, taking note of any changes in flare-up frequency. Review & record current laboratory results specific to SLE.

- ***6 months after Ad-SVF implant***: Clinical evaluation of SLE symptoms, taking note of any changes in flare-up frequency. Review & record current laboratory results specific to RA and X-ray report. Review of criteria from American College of Rheumatology.

Your doctor will contact you by phone within the first week to follow up then future follow up visits will be arranged through your patient coordinator. If you need assistance before do not hesitate to contact us.

SLE – Supporting Studies

Clin Immunol. 2013 Aug;148(2):186-97. doi: 10.1016/j.clim.2013.05.014. Epub 2013 May 30.

Hematopoietic and mesenchymal stem cell transplantation for severe and refractory systemic lupus erythematosus.

Sui W, Hou X, Che W, Chen J, Ou M, Xue W, Dai Y.

Author information

Abstract
Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by multi-organ involvement leading to significant morbidity and mortality in predominantly young women. The underlying pathogenesis involves the emergence of autoreactive T and B lymphocytes, production of autoantibodies, formation and deposition of immune complexes in various tissues leading to inflammation and organ damage. Recently, growing evidence suggests that the functions of hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) are disrupted in SLE pathology. And HSC or MSC transplantation (HSCT/MSCT) can offer an effective and safe therapy for the severe SLE patients, resulting in disease clinical remission and improvement of organ dysfunction. In this article, we provide a brief overview of current research of autologous or allogeneic HSCT/MSCT in SLE and describe our current understanding of the mechanisms by which it plays a part in treating SLE, for better understanding of the pathogenesis, diagnosis and treatment for SLE.

SLE – Supporting Studies

Klin Med (Mosk). 2011;89(5):44-9.

[Late results of high-dose immunosuppressive therapy with autotransplantation of hematopoietic stem cells in patients with severe refractory systemic lupus erythematosus].

[Article in Russian]
[No authors listed]

Abstract
The aim of the study was to assess long-term results of high-dose immunosuppressive therapy with autoimplantation of hemopoietic stem cells in patients with severe systemic lupus erythematosus (SLE) resistant to standard immunosuppressive therapy and compare them with the outcome of the two modalities. The study and control groups comprised 15 women each aged 18-55 and 20-55 years respectively. The results were estimated 1 months after the onset of therapy and during the 45 +/- 10.4 (study) and 30 +/- 7.6 (control) month follow-up. Combined treatment resulted in complete remission (SLEDAI below 3) in 6 (40%) and reduced SLE activity in 6 (40%) patients. The effect was absent in 1 (7%) patient, 2 others died. Remission and reduced SLE activity occurred in 1 (7%) and 1 (7%) patients of the control group respectively, 13 (87%) failed to benefit from therapy, and 1 (7%) died. Seven (47%) patients given combined treatment suffered recurrence of SLE, 3 (20%) had complete or partial remission, and 3 died during the long-term follow-up. Five-year survival rate was 80%. None of the patients in the control group showed remission in the late posttreatment period, SLE activity remained unaltered in 8 and progressed in 4; two patients died. Five-year survival rate was 70%. It is concluded that high-dose immunosuppressive therapy with autoimplantation of hemopoietic stem cells is an efficacious tool for the treatment of lupus erythematosus resistant to standard therapy and has advantages over the latter.

PMID: 22242267 [PubMed - indexed for MEDLINE]

SLE – Supporting Studies

Transplant Proc. 2011 Jun;43(5):1924-7. doi: 10.1016/j.transproceed.2011.03.039.

Autologous stem cell transplantation for systemic lupus erythematosus: report of efficacy and safety at 7 years of follow-up in 17 patients.

Song XN, Lv HY, Sun LX, Meng JB, Wang JK, Zhang JQ, Chang YJ.

Abstract

INTRODUCTION:

We observed the efficacy and toxicity of autologous stem cell transplantation (auto-SCT) for patients with systemic lupus erythematosus (SLE).

METHODS:

Seventeen patients with SLE were treated with auto-SCT. No prisoners were used in the study. Peripheral blood stem cells were mobilized with cyclophosphamide (Cy) and granulocyte colony-stimulating factor. After a conditioning regimen of Cy and antithymocyte globulin, we reinfused stem cells. The probabilities of overall survival (OS) and progression-free survival (PFS) were used to assess the efficacy and adverse experiences, to detect the toxicities of the treatment.

RESULTS:

The median follow-up time was 89 months (range 33-110). Probabilities of 7-year OS and PFS were 82.4% ± 9.2% and 64.7% ± 11.6%, respectively. The principal adverse events included allergy, infection, elevation of liver enzymes, bone pain, and heart failure. Two patients died due to severe pneumonia and heart failure at 33 and 64 months after transplantation, respectively.

CONCLUSIONS:

Our 7-year follow-up results suggested that auto-SCT seemed beneficial for SLE patients.

PMID: 21693301 [PubMed - indexed for MEDLINE]

SLE – References

Sui W, Hou X, Che W, Chen J, Ou M, Xue W, Dai Y. Hematopoietic and mesenchymal stem cell transplantation for severe and refractory systemic lupus erythematosus. Clin Immunol. 2013. doi: 10.1016/j.clim.2013.05.014. Epub 2013 May 30.

Song XN, Lv HY, Sun LX, Meng JB, Wang JK, Zhang JQ, Chang YJ. Autologous stem cell transplantation for systemic lupus erythematosus: report of efficacy and safety at 7 years of follow-up in 17 patients. (2011) doi: 10.1016/j.transproceed.2011.03.039.