A Phase II Study of **H**igh-Dose Immunosuppressive Therapy (HDIT) Using Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM) + Thymoglobulin, and **A**uto**L**ogous CD34+ Hematopoietic Stem Cell **T**ransplant (HCT) for the Treatment of Poor Prognosis **M**ultiple **S**clerosis (HALT MS)

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Introduction

The eradication or severe depletion of lymphoid effector cells with high-dose immunosuppressive therapy (HDIT) followed by autografting may "reset" the immune system and result in sustained remission of multiple sclerosis (MS) **(1)**. The HALT MS Protocol is a Phase II, single-arm study of HDIT and autologous hematopoietic cell transplantation (HCT) with the primary objective of determining the durability of disease stabilization in MS patients. Secondary objectives evaluate the safety and efficacy of autologous HCT, immune reconstitution, and mechanisms of disease following treatment. Tertiary objectives include the evaluation of response to treatment of the brain with magnetic resonance imaging (MRI) including magnetic transfer ratios (MTR) and magnetic resonance spectroscopy (MRS). This is a 7-year study that seeks to enroll 30 subjects over 2 years at three sites. Subjects will be followed for 5 years after HDIT.

Background

The major histological features of the lesions in the central nervous system (CNS) of patients with MS are inflammation, demyelination and gliosis. A prominent inflammatory infiltrate (lymphocytes and monocytes) occurs in the perivascular space as well as in the plaques and normally myelinated CNS. Although the etiology for the progressive neurological loss is not fully defined, evidence points to an autoimmune pathogenesis, at least in the initial stages. In the more aggressive forms of MS, a profound disability can result, and in some cases, life expectancy can be significantly shortened. In a recent study of the natural history of MS, the median time from the onset of MS to a Kurzke Expanded Disability Status Scale (EDSS) score of 7.0 was 29.9 years. However, the median times from the assignment of an EDSS score of 4.0 to a score of 6.0, and scores of 6.0 to 7.0 were 5.7 and 3.4 years, respectively. At 30–40 years after onset of the progressive phase of the disease, up to 80% of patients had an EDSS of 8.0 points or greater. None of the current treatments utilizing immunosuppressive or immunomodulatory agents are curative, although a decrease in the frequency of relapse and delay in loss of neurological function has been demonstrated.

Studies of experimental allergic encephalomyelitis (EAE), a murine model for MS, have indicated that disease control can be obtained by HDIT followed by transplantation with allogeneic, syngeneic, and autologous marrow. Previous clinical experience with allogeneic and autologous HCT suggested that long-term remissions could be achieved in otherwise incurable autoimmune diseases. The underlying hypothesis for this study is that HDIT followed by infusion of lymphocyte-depleted (CD34-selected) autologous peripheral blood stem cells (PBSC) would arrest further immune-mediated neurological damage through the elimination of autoreactive effector cells, the restoration of immunoregulatory mechanisms, or both. Early studies of HDIT and autologous HCT included MS patients with advanced disease, with EDSS scores typically between 6.0 and 8.0. Non-immunological processes may contribute significantly to loss of neurological function in patients with advanced disease from damage related to the autoimmune process in earlier stages of the disease. Accordingly, a study is proposed of HDIT and HCT in which patients with frequent relapses, failing treatment, and without advanced disease (EDSS 3.0–5.5) would be included to assess time to treatment failure over a planned follow-up of 5 years.

Early studies used different HDIT regimens including those with total body irradiation **(2-6)**. The common feature to all these studies was the intensive immunosuppression associated with the regimen and the advanced stage of disease for those MS patients included in the study. The HDIT regimen used most commonly in North America included total body irradiation, and in Europe, it was high-dose combination chemotherapy only (BEAM).

This protocol will use a HDIT regimen consisting of BEAM (carmustine, etoposide, cytosine arabinoside, and melphalan) and Thymoglobulin® (rATG) followed by HCT with autologous CD34+ cells. The combination of carmustine, etoposide, cytosine arabinoside, and melphalan has been a commonly used regimen in HCT for non-Hodgkin's lymphoma. The regimen used in this protocol was chosen to provide intensive immunosuppression prior to hematopoietic reconstitution from a lymphocyte-depleted stem cell population. Thymoglobulin will be administered in an attempt to eliminate lymphocytes that survive the preparative regimen and stem cell selection process. In the North American pilot studies, most of the experience was with TBI-containing HDIT, and the regimen was associated with a low level of acute toxicity. However, since progression was observed in some patients in these studies, the long-term risks associated with TBI were assumed greater than what was considered acceptable. The BEAM/rATG regimen has been most commonly used in Europe with acceptable safety and efficacy outcomes and is being used in the randomized multi-center Phase III European study. As Thymoglobulin is directed against lymphocyte cell populations and not other blood cell populations, it allows for increased intensity of the immunosuppressive effect without increasing other non-hematologic cytotoxicity.

In a recently reported study of the Italian experience with BEAM/rATG and autologous HCT which included 19 patients with high disease activity based on magnetic resonance imaging (MRI) and sustained clinical deterioration, all patients showed clinical stabilization or improvement **(7)**. With a median follow-up of 3 years, 3 patients subsequently deteriorated, and 1 of these was beyond the pretransplant baseline EDSS score (**Figure 1**). No active MRI lesions were detected after HDIT except in one patient at 4.5 years (**Figure 2**). Health-related quality of life was evaluated with the MSQOL-54 questionnaire showed a statistically significant improvement in both composite scores and in most individual domains (**Figure 3**). Infections were limited to the 3-month period after HDIT, and there was no treatment-related mortality. It was concluded that HDIT could induce prolonged clinical stabilization in patients with high disease activity resulting in sustained periods without treatment and improvement in quality of life.

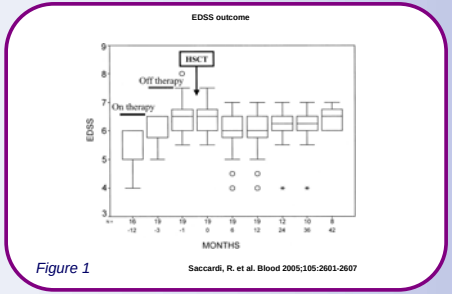

Figure 1

Saccardi, R. et al. Blood 2005;105:2601-2607

Summary of SCMS2 Protocol

Objectives:

1. The primary objective is to determine the 5-year durability of disease stabilization in MS patients after HDIT and autologous HCT.
2. The secondary objectives of the study are to evaluate the safety and efficacy of autologous HCT, immune reconstitution, and mechanisms of disease following autologous HCT for MS through a number of specific end points.
3. The tertiary objectives of the study are to evaluate myelin content and axonal integrity using magnetic resonance imaging approaches in MS patients undergoing autologous HCT.

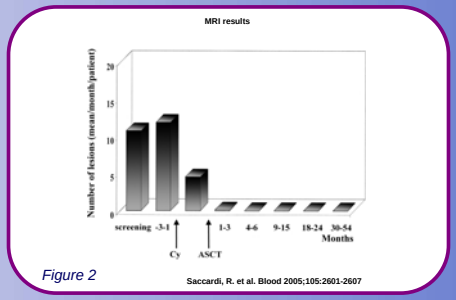

Figure 2

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End Point:

The primary end point for this study is the time to treatment failure during the 5 years after transplant. A composite end point for treatment failure is used because *(a)* mortality may occur from this protocol treatment, *(b)* MS disease activity can be asymptomatic (*i.e.,* reflected in MRI abnormalities in the absence of relapses or disability progression), and *(c)* progression in disability may occur in MS without active inflammation. A composite end point reflecting these 3 failure outcomes are appropriate for a high-risk investigational study with an aim of long-term elimination of MS disease activity.

Treatment failure is defined as death from any cause in the 5 years after transplant or MS disease activity or disability as evidenced by any of the following during the 5-year period:

1. Change in pre-transplant EDSS of 1.0 or greater as compared to the EDSS at baseline.
2. Presence of 2 or more independent MS lesions on MRI indicative of MS disease activity on brain MRI done 1 year or more after HCT.
3. Relapse defined as the development of a new neurological sign and corresponding symptom, or worsening of an existing neurological sign and symptom, localized to central nervous system white matter, resulting in neurological deficit/disability, and lasting over 48 hours.

The secondary and tertiary endpoints include the assessment of safety, other measures of efficacy and mechanistic outcomes.

Subject Selection:

➢Inclusion

This study is designed for MS patients, EDSS 3.0-5.5, with poor prognosis MS based on disease activity, poor response to treatment, and progressive disability.
Subjects who meet the following **inclusion criteria** are eligible for enrollment in the study:

1. Age between 18 and 60 years, inclusive.
2. Diagnosis of MS using McDonald Criteria.
3. MS duration < 15 years from diagnosis.
4. Relapsing remitting multiple sclerosis with cumulative disability or progressive relapsing multiple sclerosis.
5. EDSS 3.0–5.5 (Appendix B) (Functional system changes in cerebral (or mental) functions and in bowel and bladder functions not taken into consideration in determining EDSS for protocol eligibility.)
6. T2 abnormalities on brain MRI consistent with MS.
7. a) 2 or more relapses in 12 months or less on therapy with EDSS increase > 0.5, maintained for > 1 month.

   OR:

   b) 1 relapse on IFN or GA with EDSS increase > 1.0 (> 0.5 for patients with EDSS at baseline enrollment of 5.5) maintained for > 1 months plus either:

   3 or more gadolinium-enhancing lesions (brain or spinal cord) on MRI obtained 3 months after relapse

   OR:

   An average of at least 3 or more gadolinium-enhancing lesions on MRIs between 3 and 12 months after relapse.
8. On therapy at least 6 months before a relapse is counted to satisfy inclusion criteria #7.

➢Exclusion

1. Primary progressive MS.
2. Secondary progressive MS without relapses for ≥ 12 months (*i.e.,* progression without exacerbations or relapses).

Treatment:

1. Mobilization of autologous peripheral blood hematopoietic progenitor cells (HPC) with G-CSF and prednisone.
2. Selection of CD34+ hematopoietic cells using the Baxter Isolex device, and cryopreservation of the autologous graft.
3. High-dose immunosuppressive therapy with BEAM + rATG 5mg/kg.
4. Reinfusion of the cryopreserved autologous CD34-selected HPC product.

Patient Assessments:

1. Intense baseline and post-intervention evaluation of clinical and MR imaging parameters of MS as well as immune reconstitution and mechanistic studies pre-HCT, at 3, 6, 12 months and then annually until 5 years post-HCT.
2. The subjects will be followed monthly for the first 3 months following transplant, then every 3 months up to Month 12 (Year 1). Starting at Year 1, the subjects will have assessments at Months 24, 36, 48, and 60.
3. Between visits to the transplant center, patients will be contacted monthly for the first year post-transplant, and every three months thereafter, to inquire regarding any new medical problems, and changes in neurologic status or MS related medications. If the patient cannot be contacted, the patient's local neurologist will be contacted to identify the same information and to assist in contacting the patient.

Sample Size:

30 patients will be transplanted on the protocol.

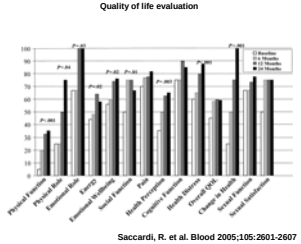

Figure 3

Saccardi, R. et al. Blood 2005;105:2601-2607

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