Immunoablation and Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis: Clinical Trial Directory

Contents

Introduction

The following directory lists past and ongoing clinical trials around the world investigating the safety and/or efficacy of immunoablation and autologous hematopoietic stem cell transplantation (IAHSCT) as an experimental treatment approach for multiple sclerosis. The specific procedure may vary from study to study, but all procedures fundamentally involve dismantling the disease-causing immune system using chemotherapy or radiation, followed by a transfusion of a participant's own stem cells to rebuild a healthy immune system that no longer attacks myelin.

Clinical Trials: Completed

1. Autologous Stem Cell Transplant for Multiple Sclerosis (MS/BMT) *

- Status: Completed
- Principal Investigator(s): Mark Freedman; Harold Atkins
- Lead Institution(s): Ottawa Hospital Research Institute
- Phase: 2
- Study Design: Non-randomized, open-label, single-group
- Enrollment: 24
- Dates:
  - Start date: August 2001
  - Completion date: December 2012
- Key Details:
  - Follow-up: 4 – 12 years
  - Eligibility:
    - 18 – 50 years old
    - EDSS: 3.0 – 6.0
    - Active MS with relapses and sustained accumulated impairment
    - Failure of previous DMTs
  - Conditioning cocktail: busulphan, cyclophosphamide and rabbit anti-thymocyte globulin
  - Primary endpoint: 3-year MS activity-free survival
  - Ex vivo CD34 immunomagnetic selection (meaning that the stem cell graft had mature immune cells removed to prevent "memory" of autoimmune response being maintained)
- ClinicalTrials.gov site
- Publications:
  - Publication (methodology)
  - Publication (results)
    - No clinical relapses
    - No new active inflammatory lesions on MRI
    - Stabilized decrease in brain volume (comparable to healthy controls)
    - No disease progression seen in 70% of participants
    - Lasting reversal of symptoms in 40% of participants

**** Funded by the Multiple Sclerosis Scientific Research Foundation***

2. Association of Nonmyeloablative Hematopoietic Stem Cell Transplantation With Neurological Disability in Patients With Relapsing-Remitting Multiple Sclerosis

- Status: Completed
- Principal Investigator(s): Richard Burt
- Lead Institution(s): Northwestern University, Chicago
- Phase: N/A
- Study Design: Case series (not a clinical trial)
- Enrollment: 123 participants with RRMS, 28 participants with SPMS
- Dates:
    - Start date: July 2003
    - Completion date: February 2014
- Key Details:
    - Follow-up: 5 years
    - Conditioning cocktail: *low-dose* cyclophosphamide, plus either alemtuzumab or thymoglobulin
    - Primary endpoint: significant change in EDSS (Improvement = +1 point or more; Progression: -1 point or more)
    - Eligibility:
        - 18 – 55 years old
        - EDSS: 2.0 – 6.0
        - Acute relapses with remission
        - Failure of previous DMTs
        - Previously treated with corticosteroids
- ClinicalTrials.gov site: N/A
- Publication (results)
    - Improvement in EDSS at 2 and 4 year time points
    - Relapse-free survival at 4 years: 80%
    - Progression-free survival at 4 years: 87%

3. High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT MS) Study

- Status: Recently completed; pending publication
- Principal Investigator(s): Richard Nash
- Lead Institution(s): Colorado Blood Center Institute
- Phase: 2
- Study Design: Single group, open label
- Estimated enrollment: 25
- Dates:
    - Start date: July 2006
    - Completion date: November 2015
- Key Details:
    - Follow-up: 5 years
    - Eligibility:
        - 18 – 60 years old
        - EDSS: 3.0 – 5.5 at baseline
        - Disease duration of < 15 years
        - Failure of previous DMTs
    - Conditioning cocktail: high dose treatment with carmustine, etoposide, cytarabine, and melphalan
    - Primary endpoint: event-free survival defined as survival without death or disease activity from any one of:
        - (1) confirmed loss of neurologic function,
        - (2) clinical relapse, or
        - (3) new lesions observed on MRI
- ClinicalTrials.gov site
- Publication (3-year interim report)
    - Event-free survival at 3 years: 78.4%
    - Progression-free survival at 3 years: 90.9%
    - Clinical relapse-free survival at 3 years: 86.3%

4. **Phase I Pilot Study of Total-Body Irradiation, Anti-Thymocyte Globulin and Cyclophosphamide Followed By Syngeneic or Autologous Peripheral Blood Stem Cell Transplantation in Patients With Multiple Sclerosis**
    - Status: Completed
    - Principal Investigators: Richard Nash
    - Lead Institution(s): Fred Hutchinson Cancer Research Center, Seattle
    - Phase: 1
    - Study Design: Uncontrolled
    - Estimated enrollment: 35
    - Dates:
        - Start date: December 1997
        - Completion date: 2001
    - Key Details:
        - Conditioning protocol: combination of total-body irradiation and cocktail of cyclophosphamide and anti-thymocyte globulin
        - Primary endpoint: Time to EDSS failure (two consecutive measures at which EDSS increased by 1 or more points
        - Eligibility:
            - 18 – 60 years old
            - RRMS, PPMS or SPMS
            - EDSS: 5.0 – 8.0
    - ClinicalTrials.gov site
    - Publications (short-term data / long-term data)
        - EDSS failure: 40% at 3 year and 52% at 6 year follow-up
        - Significant number of participants remained stable at 6 years
        - 1 relapse in 1 participant shortly after transplant

5. Immunological Mechanisms of Hematopoietic Stem Cell Transplantation in Multiple Sclerosis

- Status: Completed
- Principal Investigators: National Institute of Neurological Disorders and Stroke
- Lead Institution(s): Northwestern University and Johns Hopkins University
- Phase: 2
- Study Design: Controlled
- Estimated enrollment: 34
- Dates:
    - Start date: May 2002
    - Completion date: May 2011
- Key Details:
    - Eligibility:
        - 18 – 70 years old
        - EDSS: 1.5 – 6.5
        - Failure of previous DMTs or refused to take DMTs
        - Active relapses with progression
    - Two groups:
        - High dose cyclophosphamide and Campath-1 with AHSCT
        - High dose cyclophosphamide without AHSCT
    - Outcomes: comparison of peripheral T cell reactivities to myelin antigens before and after treatment
        -
    - Three treatment strategies: early, conventional, and salvage/late
- ClinicalTrials.gov site
- Publication: not available

6. **High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation as a treatment option in multiple sclerosis**
    - Status: Completed
    - Principal Investigators: Yury Shevchenko
    - Lead Institution(s): Pirogov National Medical Surgical Center, Russia
    - Phase: 2
    - Study Design: Unknown
    - Enrollment: 50
    - Dates:
        - Start date: 1999
        - Completion date: 2006
    - Key Details:
        - Eligibility:
            - 18 – 55 years old
            - EDSS: 1.5 – 8.0
            - New lesions on MRI
        - Primary endpoint: Improvement in neurologist symptoms (0.5+ increase in EDSS)
    - ClinicalTrials.gov site: Not registered
    - Publication:
        - 28 participants had improvement in neurological symptoms (0.5+ increase in EDSS)
        - 17 participants had disease stabilization
        - Progression free-survival: 72%
        - No new or enlarging lesions in participants without disease progression

7. **High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation as a treatment option in multiple sclerosis**
    - Status: Completed
    - Principal Investigators: Yury Shevchenko
    - Lead Institution(s): Pirogov National Medical Surgical Center, Russia
    - Phase: 2
    - Study Design: Open label
    - Enrollment: 95
    - Dates:
        - Start date: 2006
        - Completion date: 2011
    - Key Details:
        - Eligibility; 3 groups:
            - Early HSCT: EDSS 1.3 – 3.0
            - Late HSCT: EDSS 3.5 – 6.5
            - Rescue therapy: EDSS 7.0 – 8.0
            - Relapsing remitting / primary & secondary progressive MS
        - Reduced intensity conditioning regimen
        - Follow-up: up to 5 years
    - ClinicalTrials.gov site: Not registered
    - Publication:
        - Long-term disease improvement/stabilization: 80%
        - Progression-free survival at 5 years: 92% after early treatment vs. 73% after late/rescue therapy
        - No new or enlarging lesions in participants without progression

8. High Dose Chemo/Radiotherapy and Hematopoietic Stem Cell Transplant for Patients With Multiple Sclerosis

- Status: Completed
- Principal Investigators: Malcolm Brenner
- Phase: 2
- Study Design: Open-label, single group
- Enrollment: 10
- Dates:
    - Start date: April 1999
    - Completion date: August 2005
- Key Details:
    - Eligibility:
        - 18 – 60 years old
        - RRMS, SPMS or PPMS
        - EDSS: 5.0 – 7.5
        - Failure of previous DMTs
    - Conditioning protocol: whole-body irradiation, cyclosphamide, ATG and MESNA
    - Primary endpoint: unknown
- ClinicalTrials.gov site
- Publication: unavailable

9. Clinical and MRI outcome after autologous hematopoietic stem cell transplantation in MS

- Status: Completed
- Principal Investigators: A Saiz
- Lead Institution(s): University of Barcelona, Spain
- Phase: 2
- Study Design: Unknown
- Enrollment: 15
- Dates:
    - Start date: 1998
    - Completion date: 2001
- Key Details:
    - Eligibility:
        - Secondary progressive / relapsing remitting MS with progression
    - Follow-up: 3 years
    - Primary endpoint: unknown
- ClinicalTrials.gov site: Not registered
- Publication:
    - 3 year probability of progression-free survival: 85.7%
    - Disease activity-free survival: 46.4%
    - No new lesion activity on MRI

10. Autologous HSCT for severe progressive multiple sclerosis in a multicenter trial: impact on disease activity and quality of life

- Status: Completed
- Principal Investigators: Riccardo Saccardi
- Lead Institution(s): University of Florence, Italy
- Phase: 2
- Study Design: Unknown
- Enrollment: 19
- Dates:
    - Start date: 1998
    - Completion date: 2003
- Key Details:
    - Eligibility:
        - 18-55 years old
        - Secondary progressive / relapsing remitting MS
        - EDSS: 5.0 – 6.5
        - Rapid progression despite conventional DMTS
    - Follow-up: up to 6 years
    - Primary endpoints: Changes in number of MRI brain lesions, changes in EDSS, toxicity (undefined)
    - Conditioning protocol: cyclosphamide, filgrastim, BCNU, cytosine arabinoside, etoposide, melphalan, ATG
- ClinicalTrials.gov site: Not registered
- Publication:
    - Initially, all participants showed clinical stabilization or improvement; 3 subsequently deteriorated
    - Only 1 new active lesion in one participant
    - Infections limited; restricted to 3 months after procedure

11. Long-Term Outcomes After Autologous HSCT for both Progressive and Relapse-Remitting MS

- Status: Completed
- Principal Investigators: Paolo Muraro
- Lead Institution(s): Imperial College of London
- Study Design: Collection of data from 25 centers and 13 countries
- Enrollment:281
- Dates:
    - Start date: 1996
    - Completion date: 2006
- Key Details:
    - Eligibility:
        - 15-65 years old
        - Relapse-remitting MS, Progressive Relapsing MS, Primary PRogressive MS, Secondary Progressive MS
            1. RRMS (16.4%)
            2. Progressive Relapsing MS (6%)
            3. Primary Progressive MS (11.4%)
            4. Secndary Progressive MS (66.2%)
        - EDSS: 1.5-9 (Median 6.5)
    - Follow-up: minimum of 5 years
    - Primary endpoints: Progression-free survival (no increases in disability as measured using the EDSS scale)
    - Conditioning protocol: varied
- ClinicalTrials.gov site: Not registered
- Publication:
    - Halted progression in 46% of individuals at 5 years post IAHSCT
    - Progression to more likely occur in: Older versus younger people; those with progressive vs relapsing MS, people that have had more than 2 DMTs
    - Death: 8 total (2.8%)

Clinical Trials: Ongoing/Recruiting

1. **Stem Cell Therapy for Patients With Multiple Sclerosis Failing Alternate Approved Therapy- A Randomized Study**
    - Status: Ongoing
    - Principal Investigator(s): Richard Burt
    - Lead Institution(s): Northwestern University, Chicago
    - Phase: 3
    - Study Design: Randomized, parallel assignment, open label
    - Estimated enrollment: 110
    - Dates:
        - Start date: January 2006
        - Estimated completion date: December 2017
    - Key Details:
        - Follow-up: 5 years
        - Eligibility:
            - 18 – 55 years old
            - EDSS: 2.0 – 6.0
            - Failure of previous DMTs
        - Randomized groups:
            2. AHSCT with chemotherapy (cyclophosphamide)
            3. Standard treatment with convention DMT (interferon, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, or tecfidera)
        - Primary endpoint: Disease progression, defined as a 1 point increase in EDSS on consecutive evaluations at least 6 months apart and not due to a non-MS disease process.
    - ClinicalTrials.gov site
    - Publication (interim subgroup; evaluating T-cell responses)
        - Evidence for removal of autoreactive T-cell clones and development of tolerance after AHSCT versus natalizumab

2. Assessment of Bone Marrow-derived Cellular Therapy in Progressive Multiple Sclerosis (ACTiMuS)

- Status: Recruiting
- Principal Investigators: Neil Scolding; Claire Rice
- Lead Institution(s): Frenchay Hospital
- Phase: 2
- Study Design: Double-blind, randomized, crossover
- Enrollment: 80
- Dates:
    - Start date: January 2014
    - Estimated completion date: October 2018
- Key Details:
    - No immunoablation
    - Eligibility:
        - 18 – 60 years
        - EDSS: 4.0 – 6.0
        - Disease duration > 5 years
        - Disease progression not due to major relapse
    - Primary endpoint: global evoked potentials (electrophysiology)
- ClinicalTrials.gov site
- Publication: unavailable

3. **Safety and Efficacy of an Immunoablative Nonmyeloablative Conditioning Protocol for Autologous Bone Marrow Transplantation (BMT) in Patients With Multiple Sclerosis (MS)**
    - Status: Pending recruitment
    - Principal Investigators: Igor Resnick
    - Phase: 2
    - Study design: Open-label, single group
    - Enrollment: 20
    - Dates:
        - Start date: October 2015
        - Estimated completion date: October 2017
    - Key Details:
        - Conditioning cocktail: low-dose fludarabine, cyclophosphamide and alemtuzumab
        - Eligibility:
            - 18 – 65 years old
            - EDSS: 2.0 – 7.0
            - Relapsing or secondary progressive MS with significant activity
            - Disease duration > 2 years
            - Failure of previous DMTs
        - Primary endpoint: neutrophil counts, transplant related mortality,
    - ClinicalTrials.gov site
    - Publication: unavailable

Clinical Trials: Discontinued

1. **Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial**
   - Status: Terminated (difficulties with recruitment and lack of funds) / partial results published
   - Principal Investigator(s): Riccardo Saccardi
   - Lead Institution(s): University of Genova, Italy
   - Phase: 2
   - Study Design: randomized,
   - Enrollment (at time of termination): 21
   - Dates:
     - Start date: July 2003
     - Completion date: 2009 (terminated prematurely)
   - Key Details:
     - Two treatment groups:
       - Immunoablation and auto HSCT (conditioning protocol: cyclophosphamide and filgrastim, carmustine, cytosine-arabinoside, etoposide, melphalan, and ATG)
       - Treatment with Mitoxantrone
     - Eligibility:
       - 18 – 50 years old
       - EDSS: 3.5 – 6.5
       - Relapsing remitting and secondary progressive MS (with or without relapses)
       - Failure of previous DMTs
     - Primary endpoint: EDSS progression and appearance of new lesions
     - Follow-up: up to 4 years
   - ClinicalTrials.gov site: Not registered
   - Publication (partial results):
     - New MRI brain lesions reduced by 79% compared to mitoxantrone
     - Reduced annualized relapse rate
     - No change in disability progression

2. **High Dose Chemo With Stem Cell Transplant as Treatment for Multiple Sclerosis That Failed Prior Treatment**
    - Status: Terminated (insufficient recruitment)
    - Principal Investigators: Seah Lim
    - Lead Institution(s): Texas Oncology Cancer Center
    - Phase: 2
    - Study Design: Open-label, single group
    - Estimated enrollment: 50
    - Dates:
        - Start date: November 2012
        - Completion date: N/A
    - ClinicalTrials.gov site
    - Publication: unavailable

Additional Resources

- Review of autologous bone marrow transplantation studies for treatment of MS (published in 2014): **Click for full text**

- Canadian Bone Marrow Transplantation Trial **homepage**