

\*Selected, quality filtered, not subject to external review

**Issue:** The National Director of Surgery and Chief Consultant of Medicine/Surgery Services in the VA Office of Patient Care Services requested assistance from the VA Technology Assessment Program (TAP) to identify published literature on the use of autologous hematopoietic stem cell transplantation (a.k.a. bone marrow transplantation or BMT) for treatment of Multiple Sclerosis (MS), focusing on the progressive forms of the disease. The information would be used to develop clinical guidance on the use of BMT for treatment of MS in the veteran population.

TAP was requested to provide a filtered reference list of relevant research, and not a full analysis.

**Background:** According to the National Multiple Sclerosis Society<sup>1</sup>, MS is a chronic, unpredictable disease of the central nervous system believed to be an autoimmune disorder. About 85% of diagnosed patients have a pattern of MS known as relapsing-remitting that is characterized by development of symptoms followed by complete or partial resolution of symptoms; the remaining patients have a progressive form of the disease resulting in slow changes in function over time. While there is no cure for MS, treatments are available to manage the disease course, alleviate symptoms, and improve function and safety.

Disease modifying treatments that modulate or suppress the immune system are recognized strategies for altering the course of most forms of MS<sup>2</sup>. In the last decade interest in the therapeutic potential of BMT has grown as an investigational treatment for progressive forms of MS that are not responsive to conventional treatment, based on results from animal studies and early clinical research suggesting improvement of disease activity on magnetic resonance imaging and related disability from myeloablative high-dose immunosuppressive therapy followed by BMT in highly selected therapy-refractory patients. However the mechanism of BMT in MS is unknown, and the long term effect of this therapy on the frequency of relapse or progression of MS in light of its associated risks is unclear.

**Methods:** Comprehensive searches were conducted using multiple electronic databases of recent literature published primarily from 2000 through July 2006. VATAP conducted searches on MEDLINE and EMBASE through Dialog© using multiple descriptors and concepts for multiple sclerosis, bone marrow transplantation, immunosuppressive agents and immunologic factors. Also searched were several on-line databases for ongoing clinical trials on the subject: Centerwatch<sup>3</sup>; Clinicaltrials.gov; Cochrane Central Register of Controlled Trials<sup>4</sup>; Current Controlled Trials (UK)<sup>5</sup>; and the National Research Register (UK)<sup>6</sup>.

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<sup>1</sup> National Multiple Sclerosis Society. Just the Facts: 2006-2007.

<http://www.nationalmssociety.org/Brochures-Just%20the.asp> , accessed December 7, 2006.

<sup>2</sup> Fassas, A and Nash, R. Multiple Sclerosis. Best Practice & Research Clinical Haematology. 2004;17(2):247-62.

<sup>3</sup> [www.centerwatch.com](http://www.centerwatch.com)

<sup>4</sup> <http://www.cochrane.us/central.htm>

Selection criteria included systematic reviews, HTA or primary data published in English on the use of BMT for treating patients with progressive forms of MS. Primary data included case reports, uncontrolled studies and controlled trials. To reduce the amount of redundant literature available on the topic, only the most recent results from the same study group on the same question of interest were included.

**Results:** The search captured 577 references. Based on title and abstract information, no systematic reviews or HTAs were identified on the topic. TAP identified the following relevant citations (see End Reference List):

1. Three recent and comprehensive review articles (Hough 2005; Tyndall 2005; Fassas 2004) that summarize the current state of practice of the use of BMT in MS;
2. Results of phase I and II trials from international research, primarily from a multicenter register sponsored by the European Group for Blood and Marrow Transplantation (EBMT)<sup>7</sup> and from the United States;
3. Information about new phase II and III research in progress.

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<sup>5</sup> <http://www.controlled-trials.com/>

<sup>6</sup> <http://www.nrr.nhs.uk/>

<sup>7</sup> [www.ebmt.org](http://www.ebmt.org)

### REFERENCE LIST

#### Review articles

Hough, R. E., J. A. Snowden, et al. (2005). "Haemopoietic stem cell transplantation in autoimmune diseases: a European perspective." British journal of haematology. **128**(4): 432-59.

Tyndall, A. and T. Daikeler (2005). "Autologous hematopoietic stem cell transplantation for autoimmune diseases." Acta haematologica. **114**(4): 239-47.

Fassas, A. and R. Nash (2004). "Stem cell transplantation for autoimmune disorders. Multiple sclerosis." Best practice & research. Clinical haematology. **17**(2): 247-62.

#### Primary studies

Samijn, J. P., P. A. te Boekhorst, et al. (2006). "Intense T cell depletion followed by autologous bone marrow transplantation for severe multiple sclerosis." Journal of neurology, neurosurgery, and psychiatry. **77**(1): 46-50. **Location: the Netherlands**

Capello, E., R. Saccardi, et al. (2005). "Intense immunosuppression followed by autologous stem cell transplantation in severe multiple sclerosis." Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. **26 Suppl 4**: S200-3. **Location: Italy**

Saccardi, R., G. L. Mancardi, et al. (2005). "Autologous HSCT for severe progressive multiple sclerosis in a multicenter trial: impact on disease activity and quality of life." Blood. **105**(6): 2601-7. **Location: Italy**

La Nasa, G., R. Littera, et al. (2004). "Allogeneic hematopoietic stem cell transplantation in a patient affected by large granular lymphocyte leukemia and multiple sclerosis." Annals of hematology. **83**(6): 403-5. **Location: Spain**

Carreras, E., A. Saiz, et al. (2003). "CD34+ selected autologous peripheral blood stem cell transplantation for multiple sclerosis: report of toxicity and treatment results at one year of follow-up in 15 patients." Haematologica. **88**(3): 306-14. **Location: Spain**

Burt, R. K., B. A. Cohen, et al. (2003). "Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of a total body irradiation-based conditioning regimen to prevent disease progression in patients with high disability scores." Blood. **102**(7): 2373-8. **Location: Northwestern U, US**

Nash, R. A., J. D. Bowen, et al. (2003). "High-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation for severe multiple sclerosis." Blood. **102**(7): 2364-72. **Location: Fred Hutchinson, Seattle, US**

Oyama, Y., B. Cohen, et al. (2002). "Engraftment syndrome: a common cause for rash and fever following autologous hematopoietic stem cell transplantation for multiple sclerosis." Bone marrow transplantation. **29**(1): 81-5. **Location: Northwestern U, US**

Mancardi, G. L., R. Saccardi, et al. (2001). "Autologous hematopoietic stem cell transplantation suppresses Gd-enhanced MRI activity in MS." Neurology. **57**(1): 62-8. **Location: Italy**

Kozak, T., E. Havrdova, et al. (2000). "High-dose immunosuppressive therapy with PBPC support in the treatment of poor risk multiple sclerosis." Bone marrow transplantation. **25**(5): 525-31. **Location: Czech Republic**

Mandalfino, P., G. Rice, et al. (2000). "Bone marrow transplantation in multiple sclerosis." Journal of neurology. **247**(9): 691-5. **Location: Ontario, Canada**

Openshaw, H., B. T. Lund, et al. (2000). "Peripheral blood stem cell transplantation in multiple sclerosis with busulfan and cyclophosphamide conditioning: report of toxicity and immunological monitoring." Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. **6**(5A): 563-75. **Location: Duarte, California**

### **Phase II and III trials in progress**

**ASTIMS.** This Phase III study in Europe compares the efficacy of intense immunosuppression followed by autologous stem cell transplantation versus monthly Mitoxantrone in multiple sclerosis patients unresponsive to conventional therapies. Recruitment started in March 2004. Full details at:

<http://www.ebmt.org/ClinicalTrials/TrialDetail.aspx?code=ASTIMS>

**High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT MS) Study.** A Phase II Study of High-Dose Immunosuppressive Therapy (HDIT) Using Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM) and Thymoglobulin, and Autologous CD34+ Hematopoietic Stem Cell Transplant (HCT) for the Treatment of Poor Prognosis Multiple Sclerosis. Full details at: [www.clinicaltrials.gov](http://www.clinicaltrials.gov) ClinicalTrials.gov identifier NCT00288626.

**Potential of human adult bone marrow stem cells for the treatment of Parkinson's Disease and multiple sclerosis.** Ma D, Tao H, Khoo M. St. Vincent's Hospital, Sydney Australia. Additional information requested. No response.

### **VA Resources**

VA National Transplant Program [www.va.gov/transplant](http://www.va.gov/transplant)

VA Multiple Sclerosis Centers of Excellence <http://www.va.gov/ms>

**VA Technology Assessment Program  
Office of Patient Care Services (11T)  
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