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## Medical Update Memo

Revised February 18, 2005  
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### **Bone Marrow Transplantation Study Update: Participants Treated in Study to Stop MS Progression**

#### **Summary**

The Multiple Sclerosis Scientific Research Foundation is funding a multi-centre project to determine definitively whether transplanting bone marrow stem cells in people with MS can stop the disease. Led by Dr. Mark Freedman (MS neurologist) and Dr. Harold Atkins (bone marrow transplant physician), both at the University of Ottawa, the study involves 32 people with rapidly progressing multiple sclerosis who are likely to become severely disabled. Twenty-four of the participants will receive bone marrow transplantation while eight other people with the same kind of MS but who do not wish to have the procedure will be the control group. Recruitment began in October 2000. The MS Scientific Research Foundation is related to the Multiple Sclerosis Society of Canada, and receives most of its funding from the MS Society. This project is funded for \$4 million over six years.

#### **Details**

As of January 2005, 17 people with MS are enrolled in the study. One person is in the control arm and has been followed for 34 months. Eleven people have received transplants to date and their follow up periods range from three to 39 months.

Generally, the transplants have been well tolerated with mild or moderate side effects. At this point, there have been no documented MS relapses following the transplant procedure. There has been one death related to chemotherapy induced liver toxicity. The study was temporarily closed to recruitment from April 2003 to March 2004 to allow the

safety committee to review the protocol. Modifications to the study protocol have been introduced to reduce the risk of liver toxicity.

While the transplantation procedure has been done on people with MS in the United States and several sites in Europe, this is the first time that the science behind the process is being scrutinized in such detail and with the involvement of a control group. The study also targets younger patients, earlier in their disease course, who may still have reversible disabilities, and it uses a different protocol.

Bone marrow transplantation is used frequently to treat leukemia. In a very small number of people who have both MS and leukemia, it has been noted that their MS improved following the bone marrow stem cells transplant. This project should allow investigators to determine if bone marrow transplantation is an effective treatment in a group of closely matched people with MS, supporting the theories that the immune system is key to the disease. Equally important, should the procedure not fully stop the disease process, the researchers may be able to detect what triggers MS early on and discover how MS begins. They are being monitored closely for any signs of disease activity in the participants at all stages of the procedure from enrolment to the end of study three years following their transplantation. Monitoring includes: complex immune system tests and the tracking of certain immune-related genetic changes in the hope of unveiling particular genes that might contribute to genetic susceptibility.

The study is headed by Dr. Mark Freedman and Dr. Harold Atkins of The Ottawa Hospital and the University of Ottawa. Co-investigators include Dr. Jack Antel, Dr. Yves Lapierre, Dr. Amit Bar-Or and Dr. Douglas Arnold, Montreal Neurological Institute and McGill University; Dr. Pierre Laneuville, Royal Victoria Hospital and McGill University; Dr. Pierre Duquette, Notre-Dame Hospital and the University of Montreal; Dr. Rafick Sekaly, University of Montreal; Dr. Hans Messner, Princess Margaret Hospital and the University of Toronto; Dr. Paul O'Connor, St. Michael's Hospital and the University of Toronto; Dr. Isabelle Bence-Bruckler and Dr. Lothar Huebsch, both at The Ottawa Hospital.

A total of 24 people who have rapidly progressive MS will undergo bone marrow transplantation. A total of eight people with the same type of MS who decide not to participate in the study are serving as the control group.

**Disclaimer**

The Multiple Sclerosis Society of Canada is an independent, voluntary health agency and does not approve, endorse or recommend any specific product or therapy, but provides information to assist individuals in making their own decisions.

**Inclusion criteria**

- ♦ Participants will be invited to join the study on the basis of the following criteria:
- ♦ Between 18 and 50 years old
- ♦ Diagnosis of MS made by a neurology expert
- ♦ History of multiple early relapses within the first two years of disease
- ♦ Having reached Expanded Disability Status Scale (EDSS) of 3 or more within two years of diagnosis (moderate disability in one functional system; fully ambulatory)
- ♦ Having an EDSS score between 3 and 6 (intermittent or unilateral constant assistance required to walk 100m with or without resting)
- ♦ EDSS Cerebellar Functional subscore of 3 or more or EDSS Pyramidal Functional subscore of 3 or more (indicating at least partial paralysis of one side of the body [hemiparesis] or partial paralysis of the lower limbs [paraparesis] or moderate tremor of the arms, leg or trunk)
- ♦ MRI scan of the brain showing typical features of MS.

The study is coordinated through the combined efforts of The Ottawa Hospital Blood and Marrow Transplant Program and the MS Research Clinic at The Ottawa Hospital. The study also involves the MS Clinic at St. Michael's Hospital, Toronto, and the Bone Marrow Transplant Unit at the Princess Margaret Hospital, Toronto, as well as the MS Clinics at Notre-Dame Hospital and the Montreal Neurological Institute and the Bone Marrow Transplant Unit at the Royal Victoria Hospital, Montreal. Assessments for admission to the study will be carried out at the four clinics. Recruitment began in October 2000.

Participants must be able to travel to and stay in one of the treatment centre areas (Ottawa or Montreal) for periods of time during the treatment procedure and be able to return periodically for monitoring. Yearly trips to Montreal for specialized MRI scanning will also be required for non-Montreal residents. The study coordinators will assist with these arrangements.

**Bone Marrow Transplantation Procedure**

The researchers are using what is known as autologous stem cell transplantation. They "harvest" a portion of each person's own stem cells which will then be used to create a "new" immune system once they are transplanted back into the person. Powerful chemotherapy drugs are used to totally eliminate from the body the immune cells that are attacking the protective myelin coating of the central nervous system as well as removing any source of their replenishment.

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The following will take place, once a person meets the study criteria and agrees to take part in the study:

- ♦ Before receiving any treatment, participants will have an operation to remove bone marrow from their pelvis bones. It will be frozen and reserved in case it is needed to restore the immune system because of problems with regrowth of a new immune system.
- ♦ To obtain the stem cells needed to create the new immune system, participants will be given Cyclophosphamide, a chemotherapy drug, and a drug called G-CSF. It is a medication which causes the bone marrow to grow more white blood cells which then enter the bloodstream. About 11 and 12 days following the G-CSF injection, a portion of the white blood cells containing the stem cells will be collected from the bloodstream via leukopheresis (a procedure similar to plasma exchange). These stem cells will be purified to remove any trace of the old immune cells before being frozen and reserved.
- ♦ Three drugs will then be given (Busulphan, Cyclophosphamide and antithymocyte globulin) over a period of several days to destroy the participants' existing immune systems.
- ♦ Finally, the purified stem cells will be thawed and given back to each individual from whom they came in a procedure like a blood transfusion.

The entire procedure will require participants to be hospital inpatients for several weeks.

### **Risks and Side Effects**

The many potential risks and complications will be explained to each participant at several meetings before they have to decide about participating in the study. Great caution is being taken to ensure the health and safety of each treated participant, but each step of this treatment carries a risk of serious complications. These may be severe enough in a small percentage of patients to be fatal. A safety committee of experts in the field of bone marrow transplantation and MS will monitor all decisions about patient treatment for their protection. Participants in the study will be actively monitored for three years including medical examinations and periodic MRI scans.

Some of the common side effects of the treatment include back pain, muscle aches, fatigue, nausea, vomiting, diarrhea, dry mouth and temporary hair loss. More severe side effects may be serious infections and, rarely, a late life malignancy.

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**Information about the Study**

For more information about the bone marrow transplantation study, please contact the principal study coordinator:

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**MS Scientific Research Foundation**

The MS Scientific Research Foundation is related to the Multiple Sclerosis Society of Canada and receives most of its funding from the MS Society. While both organizations fund research, the MS Society also has an extensive services program for people with MS and their families. For more information, contact the MS Society at 1 800 268-7582 or [www.mssociety.ca](http://www.mssociety.ca).

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