Canadian Agency for Drugs and Technologies in Health

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Investigating Chronic Cerebrospinal Venous Insufficiency for the Treatment of Multiple Sclerosis

Environmental Scan

Context and Policy Issues

Multiple sclerosis (MS) is a neurological disease common in young adults.[1] The Multiple Sclerosis Society of Canada estimates that there are 55,000 to 75,000 people living with MS in Canada.[2] This is one of the highest prevalence rates of MS in the world. MS causes disability because of mobility and vision problems, fatigue, incontinence, and cognitive impairment.[1] The Public Health Agency of Canada estimated that the total costs associated with MS in 2000 to 2001 for hospitalization, treatment, and lost productivity due to morbidity and premature mortality was $950.5 million.[1]

There is currently no cure for MS. First-line therapies for MS, such as interferon beta and glatiramer acetate, have not been shown to consistently suppress disease progression.[3] Immunosuppressive therapies (such as, cyclosporine, methotrexate, mitoxantrone, and azathioprine) also play a role in MS therapy, but tolerability of them and their adverse effects limit their use.[3] Natalizumab is the first monoclonal antibody approved by Health Canada for the management of MS;[4] however, its use may be limited by the risk of progressive multifocal leukoencephalopathy (a serious viral infection of the brain that is often life-threatening).

Although MS is commonly believed to be an autoimmune disease, the evidence to support this concept has been questioned.[5] An alternative hypothesis has been put forth by Dr. Paolo Zamboni, a former vascular surgeon and professor at the University of Ferrara in northern Italy.

Dr. Zamboni believes a phenomenon termed chronic cerebrospinal venous insufficiency (CCSVI), an abnormality in blood drainage from the brain and spinal cord, may cause the build-up of iron deposits and contribute to inflammation and nervous system damage.[6] Initial findings that CCSVI may be associated with MS were published in 2008 from a study of 65 patients with MS.[7] Results from a second study suggested that treating CCSVI with endovascular angioplasty (the insertion of a tiny balloon or stent into blocked veins to improve blood flow), also referred to as the liberation procedure, is feasible and safe.[8]

However, results from other studies have not supported the hypothesis that CCSVI is present in patients with MS.[9,10] In March 2010, Stanford University halted endovascular treatments for CCSVI after two people experienced serious complications after the stenting of the jugular veins.[11]

As is it not known if or how CCSVI contributes to MS, rigorous large-scale clinical trials have been recommended to determine if CCSVI is a clinically important factor in the development or progression of MS.[12,13]

In light of the high prevalence of MS in Canada, the validity of the liberation procedure for MS has generated considerable interest in the medical and scientific communities and politicians have faced pressure from the public to provide funding for clinical trials.

Objectives

The purpose of this report is to provide information regarding the investigation of the liberation procedure for the treatment of MS. The following questions will be addressed:

- Which clinical trials in North America are currently studying the association of CCSVI with MS?
- What is the status of funding for CCSVI research in Canada?

Ongoing Clinical Trials

The findings of this environmental scan are not intended to provide a comprehensive review of the topic. The results of this report are based on a limited literature search. This report is based on information gathered as of November 15, 2010.

In June 2010, the National MS Society in the US and the Multiple Sclerosis Society of Canada committed more than $2.4 million to support seven new research projects focused on the role of CCSVI in MS (Appendix 1).[14] The two-year grants began in July 2010. The seven research leads have been asked to provide interim updates every six months to the Canadian and US MS societies on their grant progress.

The structure and function of veins draining the brain and spinal cord will be studied in individuals representing a spectrum of MS types, severities, and durations of disease. People with other diseases and healthy volunteers will be used for comparison. These diagnostic studies are not designed to treat CCSVI but, rather, to confirm whether CCSVI contributes to MS disease activity, to identify the best imaging technology to evaluate it, and to resolve conflicting data from previous studies. These studies may also be used to design protocols for possible exploratory therapeutic trials that may be undertaken if blockages are found.

In addition to the clinical trials funded by the MS societies, researchers at the University of Buffalo in New York are currently studying the prevalence of CCSVI in people with MS[15] and the safety and efficacy of endovascular angioplasty[16] (Appendix 1). Two other trials have also been registered for the evaluation of endovascular angioplasty in the treatment of MS.[17,18]

Investigators at McMaster University and St. Joseph's Healthcare in Hamilton, who were not funded by the Multiple Sclerosis Society of Canada, are currently raising funds through public donations for CCSVI research. [19]

Government Funding for CCSVI Research

In August 2010, the Canadian Institutes for Health Research (CIHR), the Multiple Sclerosis Society of Canada, and federal and provincial representatives met to review evidence related to the etiology and treatment of MS and to identify clinical research priorities.[20] There was unanimous agreement from the scientific experts that a pan-Canadian interventional trial should not be initiated because of a lack of scientific evidence. The following recommendations were made to the Minister of Health:

- To establish a scientific expert working group made up of the principal investigators of the seven MS society-sponsored studies, scientific leadership from CIHR and the MS societies, and a representative from the provinces and territories to monitor and analyze the results of ongoing studies.
- Based on the outcomes of the studies, the scientific expert working group should make recommendations on further studies including, if appropriate, a pan-Canadian interventional clinical trial that would evaluate the safety and efficacy of the liberation procedure in patients with MS.

On September 1, 2010, Federal Health Minister Leona Aglukkaq accepted the recommendations presented by CIHR and announced that the federal government would await the results of studies currently underway and guidance from the scientific expert working group before funding a pan-Canadian clinical trial.[21]

Provincial Ministries of Health in Manitoba, Quebec, Nova Scotia, and Prince Edward Island have all expressed interest in supporting a pan-Canadian clinical trial, provided that the evidence from ongoing studies is positive.[22-25] Manitoba has set aside $500,000 to allow the province to move quickly if evidence from ongoing studies supports the move to clinical trials.[22]

In October 2010, Saskatchewan invested $5 million to fund province-based clinical trials, which are expected to begin in April 2011.[26] The Saskatchewan Health Research Foundation will develop the call for clinical trials and provide the scientific, ethical, and financial expertise to manage this initiative on behalf of the government.[27] This decision was made despite a statement from Manitoba Health Minister Theresa Oswald that a "patchwork" approach of small provincial trials may lead to conflicting results.[28] Saskatchewan Health Minister Don McMorris commented that he is skeptical that the federal, provincial, and territorial governments will commit to CCSVI research in the near future, prompting the provincial initiative.[29]

Similarly, Newfoundland and Labrador has devoted $320,000 to fund a provincially based observational study to track the progress of patients who travel overseas at their own expense to have the liberation procedure.[30] Participants will receive a magnetic resonance imaging exam before the procedure and will be followed-up by local neurologists to collect data on their condition.

On November 24, 2010, New Brunswick Premier-elect David Alward, announced during his throne speech, to create a $500,000 fund to help MS patients receive the liberation procedure.[31] How the fund will be dispersed is still being worked out, but the intent is for the money to be matched by contributions from the public.

Ontario is waiting for more scientific research and consensus in the scientific community before proceeding with funding for clinical trials.[32]

Alberta's Health Minister Gene Zwozdesky has established a working group to improve coordination of programs and services to patients with MS. Minister Zwozdesky has also held a meeting with researchers, MS advocates, patients, and medical experts to discuss what Alberta can do to help accelerate research in the area of MS and possible treatments, including the liberation procedure. In August 2010, Alberta Health Services issued a position paper challenging the validity of findings published by Dr. Zamboni and cautioning MS patients about seeking the liberation procedure.

A statement from Health Minister Glenn Hart in October 2010 indicated that the Yukon territorial government will not be providing financial support for clinical trials.[33]

Since the CIHR recommendation, the Multiple Sclerosis Society of Canada has announced it is reserving $1 million for a pan-Canadian therapeutic clinical trial if preliminary results indicate that such a trial is warranted.[33] The organization hopes to work with the provinces and federal government to secure the remaining funds if the trial is approved.

Other Emerging Technologies

In September 2010, fingolimod (a sphingosine-1-phosphate analog) was approved by the Food and Drug Administration as the first oral disease-modifying therapy for MS.[34] Cladribine (a purine nucleoside analog) was granted a priority review designation by the Food and Drug Administration in July 2010.[35]

Health technologies currently being studied in clinical trials for MS include monoclonal antibodies (such as rituximab, daclizumab, alemtuzumab, ocrelizumab, and ofatumumab), statins (such as atorvastatin and simvastatin), laquinimod, oral fumarate, teriflunomide, firategrast, and autologous hematopoietic stem cell transplantation.[3,36,37]

Conclusions

It is not yet established whether CCSVI contributes to MS disease activity, and there have been conflicting data as to the frequency of this condition in people with MS. It is hoped that findings from ongoing studies will provide clarity regarding the need for pan-Canadian therapeutic clinical trials. Scientific and medical organizations and experts across Canada have uniformly urged caution and rigorous study before the liberation procedure is recommended for use, particularly considering the other emerging health technologies that are currently in the pipeline for the management of MS.

Complementing this environmental scan, CADTH prepared, in December 2009, a rapid response on surgical procedures targeting CCSVI for the treatment of MS. This is available free of charge on the CADTH website.[38]

North American Guidelines and Recommendations

Canadian Institutes of Health Research and Multiple Sclerosis Society of Canada. Joint Invitational Meeting on Multiple Sclerosis Research- Summary Report, August 2010. http://www.cihr-irsc.gc.ca/e/42381.html

Interventional Endovascular Management of Chronic Cerebrospinal Venous Insufficiency in Patients with Multiple Sclerosis: A Position Statement by the Society of Interventional Radiology, Endorsed by the Canadian Interventional Radiology Association, August 2010. http://www.sirweb.org/news/newsPDF/SIR_MSstatement_JVIR.pdf

Ontario Ministry of Health and Long-Term Care for the Ontario Health Technology Advisory Committee. Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency, May 2010. http://www.health.gov.on.ca/english/providers/program/ohtac/tech/recommend/rec_ccsvi_20100611.pdf

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Appendix 1: Ongoing CCSVI Clinical Trials in North America

Investigator, Location	Study Information	Funding
Canada		
Dr. Brenda Banwell, Hospital for Sick Children, Toronto. [39]	The study will use MRI and novel measures of venous flow to determine if CCSVI occurs in the veins of children and teenagers with MS. A total of 60 participants, both healthy and with MS, will be enrolled. This population will allow an examination of disease process at an early stage where other health conditions that might affect blood flow do not exist.	Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society
Dr. Fiona Costello, Hotchkiss Brain Institute, University of Calgary.[40]	This controlled study will examine vein drainage in a cross-section of people with MS compared with healthy volunteers. The team will assess if linkages exist between venous abnormalities and different aspects and measures of MS activity and tissue damage. A total of 180 participants will be enrolled. Ultrasound, as originally used by Dr. Zamboni, and magnetic resonance studies of the veins will be used.	Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society
Dr. Carlos Torres, Ottawa Hospital, University of Ottawa.[41]	The study will use 3-Tesla MRI and Doppler ultrasound technology to explore differences in the anatomy of veins in the neck, chest, and spine and to assess iron deposits in the brain. The study will include 50 people with MS and 50 age-matched healthy volunteers.	Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society
Dr. Anthony Traboulsee, MS Clinic at UBC Hospital, Vancouver Coastal Health and University of British Columbia, Vancouver. Dr. Katherine Knox, Saskatoon MS Clinic, University of Saskatchewan, Saskatoon.[42]	The prevalence of CCSVI in 200 people with and without MS will be studied using catheter venography, ultrasound, and magnetic resonance venography. The study allows the inclusion of family members of the MS patient, such as identical twins, in the control group. The research aims to determine the reliability and accuracy of different imaging techniques for screening of CCSVI.	Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society
United States		
Dr. Aaron Field, University of Wisconsin School of Medicine and Public Health Madison, Wisconsin. [43]	The study will use MRI scans to generate detailed images of veins in the head and neck in 112 people with MS, 56 controls without MS, and 56 people with other neurological conditions. These images will be compared with results obtained from the ultrasound techniques used by Dr. Zamboni.	Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society
Dr. Robert Fox, Cleveland Clinic Foundation Cleveland.[44]	The study will compare 90 people with MS to 80 healthy volunteers. The team will use the ultrasound techniques used by Dr. Zamboni, as well as magnetic resonance studies of the veins, MRI scans of the brain, and clinical measures to determine MS activity. To distinguish if vein abnormalities are from atrophy (brain-tissue	Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society

Investigator, Location	Study Information	Funding
	volume loss) and not specifically MS, the study is also comparing the MS group to people with atrophy from Alzheimer disease. Neck and spinal cord tissue from MS patients obtained through autopsy will be used for tissue-based evaluation of CCSVI and its possible relationship to MS.	
Dr. Jerry Wolinsky, University of Texas Health Science Center, Houston.[45]	This study will replicate the ultrasound methods used by Dr. Zamboni to investigate the association of CCSVI with major clinical types of MS using non-MS control groups. A total of 275 people will be recruited. The team will also assess whether other imaging methods can confirm the ultrasound findings and which technique is the most reliable to screen for CCSVI.	Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society
Buffalo Neuroimaging Analysis Center, University of Buffalo, New York.[46]	This blinded randomized controlled trial is investigating the prevalence of CCSVI in patients with MS when compared with healthy controls or controls with other neurological disorders. Preliminary results of the first 500 of 1,000 participants were released in February 2010 and show that 56.4% of participants with MS exhibited evidence of CCSVI compared with 22.4% of healthy controls.[47] Complete data from the first 500 participants will be presented at the American Academy of Neurology in April 2011.	University of Buffalo Neuroimaging Analysis Center of the Jacobs Neurological Institute
Dr. Adnan Siddiqui, University of Buffalo, Department of Neurosurgery, New York.[16]	This randomized, double-blind study will test the safety and efficacy of interventional endovascular therapy. In the first phase, 10 MS patients exhibiting CCSVI will undergo minimally invasive venous angioplasties to determine if the procedure can be performed safely. The second phase will randomize 20 MS patients to undergo either venous angioplasty or a "sham angioplasty" (i.e., catheter is inserted, but there is no inflation of the balloon). If the results are positive, the researchers will approach the University of Buffalo Institutional Review Board for an extension of the protocol to study a larger group of patients.	Not stated
Dr. Gary Siskin, Albany Medical Center, New York.[17]	This double blind, randomized controlled trial will determine if venous angioplasty is an effective treatment for CCSVI and it is expected that the study will enrol approximately 130 patients. The outcomes of two groups of patients will be compared. The first group will have CCSVI diagnosed on a venogram and treated with angioplasty and the second group will have CCSVI diagnosed on a venogram and treated with a sham procedure. Several outcomes will be evaluated over 24 months, including safety, efficacy, and quality of life.	Community Care Physicians, P.C.

Investigator, Location	Study Information	Funding
Dr. Manish Mehta, The Vascular Group, PLLC; and The Vascular Health Pavilion Albany, New York.[18]	The study is a randomized, double-blind (sham procedure), placebo-controlled, feasibility clinical trial with an expected enrolment of 600 patients. The purpose is to evaluate the safety, feasibility, and efficacy of percutaneous transluminal angioplasty in treating extracranial venous obstructive lesions, and its influence on the clinical outcomes of MS patients who have been found to have CCSVI. Outcome measures evaluated over 24 months include adverse events, neurological assessment, MRI evaluation of MS lesions, and mortality.	The Vascular Group, PLLC

CCSVI = chronic cerebrospinal insufficiency; MRI = magnetic resonance imaging; MS = multiple sclerosis.

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