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RESEARCH/CLINICAL UPDATE

cc: Chapter President, Programs, Development

July 20, 2012

Study Suggests that Interferons Did Not Reduce MS Progression

In a study looking at more than 2,000 people enrolled in MS clinics in British Columbia, there was no reduction in MS progression in people treated with interferon beta compared to untreated controls. This study did not address the value of interferon beta in reducing MS relapses and the development of lesions (tissue damage) or improving quality of life in people with MS. While the results are at variance with other recent research and need to be confirmed, this carefully conducted study presents some evidence that there is an unmet need for treatments that reduce the likelihood of MS progression. Research also is needed to find more comprehensive and better tools to measure the effectiveness of MS treatments. Afsaneh Shirani, MD, Helen Tremlett, PhD, and colleagues (University of British Columbia, Vancouver, Canada) report the findings in the *Journal of the American Medical Association* (2012;308(3):247-256, <http://jama.jamanetwork.com/article.aspx?articleid=1217239>). This study was supported by the Canadian Institutes of Health Research, the National MS Society, the MS Society of Canada and others.

Background: Multiple sclerosis involves immune system attacks against the brain and spinal cord. Several treatments, called disease-modifying therapies (DMDs, <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/index.aspx>), are available that can reduce the inflammation associated with the immune attack and reduce disease activity, such as relapses and the development of new lesions. The effect of these therapies on damage to nerve fibers is not well understood, and it is controversial to what extent they reduce the progression of MS, which is associated with nerve fiber damage. Data on MS progression comes largely from what is reported from relatively short-term clinical trials. Some of the difficulties involved in answering this question using traditional, randomized clinical trials include the fact that it would take a long time to observe effects on progression, and that the conditions of a trial do not necessarily reflect the 'real world' of treatment and how it might affect disease progression.

The study: The investigators collected information from the British Columbia MS database, which captures about 80% of all people with MS in British Columbia and links the four MS

clinics in that province. They observed people with relapsing MS who had registered with a clinic between April 1985 and December 2004 and who were eligible for interferon beta treatment. Within this group, they compared 868 people who were treated with interferon beta, 829 people who were not treated, and 959 historical controls (people who were untreated before approval of interferons for MS). The main outcome measure was time to a confirmed and sustained EDSS (a scale used to measure MS-related disability) score of 6. This score indicates “intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting.”

The results indicated that those treated with interferon were just as likely to progress to an EDSS of 6 as those who were untreated. The lack of difference among patients persisted whether controls were contemporary or historical, or whether an EDSS of 4 rather than 6 was considered. However, the authors point out that this study is not capable of discerning a subgroup of patients who might indeed experience reduced progression through interferon use.

Comment: In an accompanying editorial, Tobias Derfuss, MD, and Ludwig Kappos, MD (University Hospital, Basel, Switzerland) point out that the comparison groups used in this study might have tended to underestimate a possible long-term benefit of treatment. They also comment that although this study was methodologically sound, it is subject to the inherent challenges of an “observational” study. In this type of study, researchers infer their conclusions based on observing treated versus untreated patients, as opposed to a randomized, placebo-controlled trial, where the researchers assign patients to either active treatment or a placebo. The results are not likely to stop the debate over the long-term effectiveness of DMDs, including interferons, on MS progression. Recently, Italian researchers using novel study design found that MS treatments were associated with a reduction in MS progression. (Read more (<http://www.nationalmssociety.org/news/news-detail/index.aspx?nid=6578>))

The Canadian study’s findings on longer-term benefits of interferons do not negate their proven value for reducing MS relapses, which have been linked to long-term progression, and the development of lesions (tissue damage). Important research is underway to help determine which people may respond best to interferons; success would help guide treatment decisions by people with MS and their health care providers, and pave the way for personalized medicine in multiple sclerosis. Research also is underway to address the need to find more comprehensive and better tools to measure the effectiveness of MS treatments. Novel imaging technology and refined clinical measures may help to capture the full spectrum of MS-related damage, and may improve our understanding of how both currently approved and experimental therapies affect MS progression.

Read more (<http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/index.aspx>) about MS treatment.



Read more (<http://www.nationalmssociety.org/research/stop/index.aspx>) about efforts to stop MS in its tracks and restore function (<http://www.nationalmssociety.org/research/restore/index.aspx>) to people with MS.



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Researchers Suggest Immune B Cells from People with MS May Produce Substances That Are Toxic to Brain Cells

Researchers have found evidence that immune cells known as B cells from people with MS may produce toxic factors that harm brain cells, in particular, cells that make myelin, the key substance needed for nerve transmission. If this factor (or factors) can be identified and confirmed to play a role in MS disease progression, it may serve as an important target for developing new MS therapies. Robert Lisak, MD, and colleagues at Wayne State University (Detroit, MI) and collaborators in Montreal, Canada report their findings in the *Journal of Neuroimmunology* (<http://www.sciencedirect.com/science/article/pii/S016557281200063X>). The study was supported by many sources including a National MS Society Collaborative MS Research Center Award, the Canadian Institutes of Health Research, and the MS Society of Canada.

Background: Multiple sclerosis involves immune system attacks against the brain and spinal cord, particularly myelin (the substance that surrounds and supports nerve fibers). B cells are one type of immune cell, and one of their roles is to make and secrete antibodies, which are substances that fight off infection in healthy people but that also can cause disease. B cells are more active in the blood and brain of people with MS, and evidence suggests that they contribute to myelin damage in MS, although their exact role is unclear. In clinical trials, a therapy (rituximab) that targets B cells reduced MS relapses and brain lesions in people with MS, and this approach with a related drug is in clinical trials.

The study: Dr. Lisak and colleagues obtained B cells from the blood of seven people with relapsing-remitting MS and four healthy controls. After growing the B cells in lab containers, they removed the cells and tested the culture medium (the liquid in which they grew), which allowed them to test the substances made by the B cells. They then isolated brain cells from rats, including oligodendrocytes, the cells that make myelin. They added the B cell culture

medium to these cells and looked at the effects on the different types of brain cells. When they added B cell culture medium from people with MS, substantially more oligodendrocytes died than when they used B cell culture medium from healthy controls.

Moreover, following addition of the B cell culture medium from people with MS, the team observed changes in the appearance of other types of brain cells known to interact with oligodendrocytes in the brain. Thus, Dr. Lisak and colleagues concluded that B cells secrete a previously undescribed substance that appears to be toxic to oligodendrocytes, and does not appear to be an antibody. This toxic substance may directly impact the oligodendrocytes and/or indirectly impact these myelin-making cells through the actions of other cell types.

Comment: Although B cells and the substances they make and secrete are known to have detrimental effects on myelin, this study provides new insight into how these effects may occur. If the toxic substance (or substances) produced by B cells can be identified and confirmed to play a role in MS, it may serve as an important target for developing new MS therapies. In the future, it may also become possible to stimulate B cells to turn off the production of this toxic factor in people with MS.



Read more (<http://www.nationalmssociety.org/research/stop/index.aspx>) about efforts to stop MS in its tracks.



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Stress Management Reduces MRI-Detected Disease Activity in New Study of People with MS

A 24-week stress management program reduced disease activity on MRI scans significantly more than in a control group, in a study of 121 people with relapsing MS. However, the benefits appeared to disappear after the weekly in-person stress management sessions were completed. David C. Mohr, PhD (Northwestern University Feinberg School of Medicine, Chicago) and colleagues report their findings in *Neurology* ([2012;79:412–419](#)). Future studies should provide more clarity for optimizing the potential benefits of stress management in people with multiple sclerosis.

Background: Many people with MS say they experience more symptoms during stressful times. When the stress abates, their symptoms seem less troubling or less severe. Research has shown a relationship between stress and the onset of MS, MS relapses and the development of new brain lesions, but a causal relationship has not been demonstrated.

The study: A total of 121 people were randomly assigned to a stress management program, or to a control group. The stress management program consisted of 16, 50-minute individual sessions with a licensed psychologist over 24 weeks, and included teaching problem-solving skills, relaxation, and enhancement of social support. The treatment was supported by a workbook for participants and therapists were guided by a treatment manual, both of which have been published. Participants were then followed for up to six months post-treatment. The control group was wait-listed for 10 months, and then participated in a five-hour workshop on stress management.

The primary goal of the study was to determine the effects of the stress management program on reducing disease activity as observed on MRI scans. The study was not designed to detect impacts on actual clinical symptoms or relapses. Secondary goals included determining the

effects on reducing stress, reducing relapses, improving disease symptoms, and safety. The study was funded by the National Institute of Child Health & Human Development.

Disease activity on MRI scans was reduced significantly among people receiving the stress management program compared to those in the control group: 77% remained free of active brain lesions (gadolinium-enhancing lesions, indicating areas of active disease) versus 55% of those in the control group; and 70% remained free of new areas of damage, versus 43% of the control group. These differences were not apparent at follow-up, once the stress management program stopped. Measures of stress reduced significantly in the treatment group, but not in the control group. There were no serious adverse events.

The authors speculate about why the benefits of the stress management treatment did not last beyond the 24-week treatment period. One possibility they point out is that participants may require longer treatment to learn to maintain the stress-reducing behaviors on their own. Another possibility is that the benefits of the stress management program were derived less from the stress management techniques and more from the positive attention they received from in-person sessions with a psychologist.

Comment: The authors are continuing to examine these results, and note that future studies in this area should include a larger trial capable of evaluating clinical outcomes. They also suggest that the use of telephone, internet, and mobile phone interventions may help sustain the results of stress management programs after the program stops, since "...long-term standard behavioral intervention can be burdensome for patients who must make weekly office visits," they write.

In an accompanying editorial, Christoph Heesen, MD, and Stefan Gold, PhD (University Medical Center Eppendorf, Hamburg, Germany) note that this study may provide the first direct evidence "for a causal link between stress and inflammatory activity in these patients." They also suggest that the study shows that science needs to be more mindful of "a biopsychosocial model of disease." This model acknowledges that biological *and* psychological factors contribute to diseases such as MS. "...the evidence for the relevance of experiences, expectations, and behavior on brain functioning is growing," they write.

Read more (<http://www.nationalmssociety.org/living-with-multiple-sclerosis/healthy-living/stress/index.aspx>) about reducing the impact of stress on MS.



Read more (<http://www.nationalmssociety.org/research/stop/index.aspx>) about efforts to stop MS in its tracks.