

Medical Update Memo

June 3, 2010

Progress on Experimental Therapies for MS, CCSVI Forum, and Much More, Reported at the American Academy of Neurology Meeting

Summary

More than 10,000 researchers and practicing neurologists from around the world gathered at the 62nd Annual Meeting of the American Academy of Neurology (AAN) in Toronto from April 10-17. Nearly 500 presentations related to research efforts to stop multiple sclerosis, to restore function, and to end MS forever. National MS Society grantees were among those presenting novel findings on many different aspects of MS research.

Details

RESEARCH TOWARD STOPPING MS

-- Experimental Therapies in the Pipeline

- **Alemtuzumab and disease progression:** In previously reported phase 2 studies, treatment with alemtuzumab (Genzyme Corporation) reduced the accumulation of disability and the frequency of relapses in 223 people with early relapsing-remitting MS, compared to Rebif. Those taking alemtuzumab, an immune-suppressing monoclonal antibody, experienced adverse events more frequently, including a serious bleeding disorder and thyroid problems. Four-year follow up among 176 of these patients shows that a greater proportion of those in the alemtuzumab group are relapse-free and have not had sustained disability progression (as measured by a 1- to 1.5-point increase on the EDSS scale, sustained for 6 months). No additional adverse events were reported. Phase III studies of alemtuzumab are ongoing, and have completed enrollment.

- **Teriflunomide results:** Mark Freedman, MD (University of Ottawa) and colleagues reported on phase II results of a study in which two doses of oral teriflunomide (sanofi-

aventis), an immune modulator, or placebo, were added to ongoing Copaxone therapy in 123 people with RR MS. Disease activity as observed on MRI scans was reduced significantly more than placebo in both treatment groups. Six people in the treatment groups had increased liver enzymes. Phase III studies of teriflunomide are underway in relapsing MS and in people at high risk for MS.

- **Omega 3-fatty acids:** Kjell-Morten Myhr, MD, PhD (University of Bergen) and colleagues randomly assigned 92 people with RR MS to receive omega-3 fatty acids (fish oil) or placebo (corn oil) capsules daily for 6 months. Thrice weekly interferon beta-1a was then added on in both groups for another 18 months. MRI scans (taken monthly until month 9 and then at months 12 and 24) and clinical outcomes were monitored. The primary outcome was the cumulative number of newly active (contrast-enhancing) lesions and did not differ between the groups. There were no differences in relapses or any of the clinical outcome measures, or of self-reported fatigue or quality of life measures. This well-designed study showed that omega-3 fatty acid supplements were safe in this group of people with MS, but failed to show benefit.

- **Mesenchymal (adult) stem cells:** Mesenchymal stem cells derived from the bone marrow potentially have the ability both to treat immune disorders and promote tissue repair. Dimitrios Karussis, MD, PhD (Hadassah Medical Center) and colleagues conducted a study of mesenchymal stem cell infusion in 15 people with MS and 19 people with the neurodegenerative disease ALS. No major side effects were reported during 25 months of follow up; 21 people experienced infusion-related side effects consisting of transient, mild fever and headache. An anti-inflammatory immune response occurred within 24 hours after infusion. There was a trend to clinical improvement, but the study was not powered to detect clinical benefit. Larger and longer-term studies are needed to determine the safety and effectiveness of this strategy.

- **Lipoic acid:** One approach to stopping MS is to find a way to protect nervous system tissues from harm. In a study supported by the National MS Society, Department of Veterans Affairs and others, Priya Chaudhary, PhD and colleagues at the Oregon Health & Science University (Portland, Oregon) investigated the neuroprotective capabilities of lipoic acid, an antioxidant that previous studies suggest can benefit mice with MS-like disease in part by inhibiting immune cells from entering the brain. In an experimental mouse model of acute optic neuritis, they found that lipoic acid could reduce damage to myelin and to nerve fibers, and also reduced inflammation. This group is planning more research needed to determine whether lipoic acid may provide benefits for people with MS.

- **T cell vaccination:** This strategy aims to induce immunity to attacking T cells. Rivka Abulafia-Lapid, PhD (Hadassah Medical Center) and colleagues randomly assigned 26

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people with progressive MS to receive either vaccination with their own “deactivated” T cells, or sham injections. They were followed for one year. Disability scores worsened slightly in the sham group and improved slightly in the vaccination group. Annualized relapses were reduced from a mean of 0.82 to 0.06 in the treatment group and remained unchanged in the sham group. MRI results did not differ between the groups. This study provides some preliminary evidence suggesting clinical benefit, but larger, controlled studies are necessary.

-- Progressive multifocal leukoencephalopathy (PML) and natalizumab:

During a plenary session, David Clifford, MD (Washington University School of Medicine, St. Louis, Mo.), who has studied and treated PML in non-MS populations and who has served as an expert consultant to Biogen Idec on this issue, presented information regarding cases of PML that have occurred in people taking natalizumab. To date, 46 cases of PML associated with natalizumab treatment since the drug re-entered the market. Identification of PML cases in the MS population can only be pursued through clinical monitoring, particularly for changes in personality or thinking, or progressive neurological impairments over weeks to months. He noted that many local labs can't detect the JC virus in spinal fluid in suspected cases because it is at very low levels, and that ultrasensitive JC DNA PCR assay may be necessary for proper detection. He also noted that although three-fourths of individuals have survived after this form of PML, most have been left with serious disability.

It is believed that most adults harbor the virus that causes PML, apparently controlled under normal circumstances by the person's immune responses. As of yet, there is no reliable way to identify individuals with MS who receive natalizumab and who might be at increased risk of PML, since it is not certain whether risk is randomly related to exposure or involves particular risk factors that are currently unknown. A presentation of a study by Leonid Gorelik, PhD, and colleagues at Biogen Idec described a new blood serum test that would detect antibodies to the JC virus, which causes PML. (The presence of antibodies indicates that a person has at some point been infected by the virus.) The team has tested 800 serum samples and has found that this test can distinguish between people with MS who are negative for antibodies (about 40 to 50%) and those who are positive (about 50 to 60%). Further work is being undertaken to evaluate the test prospectively in patients receiving natalizumab to see if a positive antibody test identifies those at risk for natalizumab-associated PML. If these studies confirm that only those with antibodies to JC virus detectable by the test are at risk of PML, those with negative tests might be considered to have little risk of the disease. (Abstract S31.003)

-- Stopping Relapses

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- **When is the first MS attack?** Olivier Gout, MD (Foundation Rothschild, Paris, France) and colleagues gave a self-administered questionnaire to 178 patients during an initial consultation with a neurologist after experiencing what was possibly a first neurologic symptom indicative of myelin damage. The neurologist validated the reported symptoms in a follow-up visit. The investigators reported that as many as 33% of the patients had prior symptoms suggestive of demyelination that went unnoticed, and that almost 70% had previous signs and symptoms that qualified them for a diagnosis of MS. They concluded that the questionnaire could facilitate earlier diagnosis and treatment.

- **In vitro fertilization (IVF) and relapses:** Laure Michel, MD (INSERM, Nantes, France) and colleagues from institutions across France reported on 28 women with MS who had undergone 64 in-vitro fertilization procedures, finding an increase in relapses within two months after the procedure. The increase was linked to both the type of hormones used (LHRH agonists, not LHRH antagonists) and to the failure of the procedure. This adds evidence to previous reports showing that IVF and other fertility procedures may increase the risk of relapse in women with MS.

- **Breastfeeding and relapses:** The risk of MS relapse is known to increase during the three months after a woman gives birth. Last year a study from San Francisco suggested that women who exclusively nursed their children were less likely to have a relapse in the year following birth, compared to women who combined nursing with bottle feeding or who chose to resume disease-modifying therapy and not to nurse. In this larger prospective study of 302 pregnancies, Emilio Portaccio, MD (University of Florence, Italy) and co-investigators at 21 MS centers in Italy did not find clear-cut evidence that breastfeeding could protect against postpartum relapses after accounting for other factors such as age, duration of disease, disease activity prior to pregnancy, and disability status. They found that the strongest predictors of relapses following a pregnancy were relapse activity preceding and during pregnancy, and the use of disease-modifying therapies prior to pregnancy, which might represent people with increased MS activity. Further research on the influence of hormonal and immunological events related to pregnancy, and their impact on the course of MS, continues to be an important area of investigation. (Abstract S40.003)

RESEARCH TOWARD RESTORING FUNCTION

-- Addressing symptoms

- **Sleep disorders and fatigue:** Christian P. Veauthier, MD (Klinikum Stralsund) and colleagues used polysomnography – a diagnostic tool used in sleep medicine – to evaluate people with MS and fatigue. They found that 25 of 26 people reporting higher levels of fatigue actually had sleep disorders, such as insomnia, restless legs syndrome or sleep apnea. Twelve had two different sleep disorders. In 40 people with lower levels of

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fatigue, 20 were diagnosed with mild sleep disorders. The group urged health care professionals treating people with MS to evaluate fatigued patients for the presence of sleep disorders, which are likely to improve with the appropriate treatments.

- **Donepezil for memory problems:** Problems with memory and thinking speed commonly affect people with MS, and studies have looked at drugs used to treat memory disorders in Alzheimer's disease to see if they would help people with MS. Several years ago, small studies of donepezil (Aricept®, Eisai Inc. and Pfizer Inc.) suggested modest benefit on some tests of cognition. In this larger, randomized, placebo-controlled, prospective trial funded by the National Institutes of Health, Lauren Krupp, MD (State University of New York, Stony Brook) and colleagues administered donepezil or inactive placebo to 120 people with all types of MS who had at least a mild memory deficit. The drug showed no benefit compared with placebo on cognitive measures or on patients' own reports of memory changes. A similar study of another Alzheimer's drug, memantine, last year also failed to show benefit. Results suggest that the mechanisms underlying cognitive impairment in MS may differ significantly from those in Alzheimer's disease .

- **Bone health:** Nancy Hammond, MD (University of Kansas Medical Center) and colleagues examined the questionnaires and bone health exams of 60 women with relapsing-remitting MS who were recruited into a larger study on bone health: 53% reported that they did no weight-bearing exercise; 15% were current smokers; 78% reported current alcohol use; 41% took some type of calcium supplementation; 45% subjects took vitamin D supplementation; and 46% reported exposure to corticosteroids. Based on the results, the investigators suggest that health care providers advise people with MS on how lifestyle can impact bone health.

- **Omega-3 for depression:** Lynne Shinto, MD (Oregon Health & Science University) and colleagues administered 6 grams/day of omega-3 fatty acids (fish oil) or inactive placebo (soybean oil) to 31 people with MS who had mild to moderate depression for three months. Both groups improved on the depression scale; there were no significant differences. However, the omega group did improve significantly more than the placebo group on a measure of cognition (PASAT). Further study is necessary to confirm this finding.

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-- CCSVI Preliminary Results

- **Buffalo CCSVI prevalence study:** In February the University at Buffalo Medical Center released preliminary results from an ongoing Combined Transcranial and Extracranial Venous Doppler Evaluation study. Using Doppler criteria developed by Dr. Zamboni, it is designed to evaluate the prevalence of venous obstruction, with a planned enrollment of 1700 consecutively recruited people who have possible and/or definite MS, other neurological conditions, and healthy controls. They are also using MRI of the brain, and in a subgroup, MRI of the veins of the neck to help verify the Doppler results.

A poster presentation by Robert Zavidinov, MD, and colleagues was based on the first 500 participants enrolled. Of those, 499 were eligible for statistical analysis: 289 people had MS, most with the relapsing-remitting form. There were 163 healthy controls, 21 with CIS (first neurological episode, at risk for developing MS) and 26 with other neurological disease. Doppler scan results were reported on five specific criteria that affect venous blood flow. Patients who met at least two of the criteria were considered to have CCSVI. 56.1% of the MS cohort met the criteria for CCSVI. This was also true for 22.7% of the healthy controls, and 42.5% of people with other neurological conditions; abnormalities were less frequent and less specific than in the original reports of Dr. Zamboni. The investigators concluded that further blinded studies are needed to determine the prevalence of CCSVI in MS.

RESEARCH TOWARD ENDING MS FOREVER

- **MS Genes on the Web:** Understanding how a person's genes make them susceptible to developing MS will go a long way toward finding ways to prevent it. Christina M. Lill, MD (University of Boulder) and colleagues reported on the new Web site www.msgene.org, a collection of published genome-wide MS studies, launched by the International MS Genetics Consortium and hosted by the Alzheimer Research Forum Web site. Site developers have systematically summarized over 800 MS genetic association studies testing over 2000 genetic variations. They list the strongest associations, which were exerted by immune system genes such as HLA-related variations, and IL7R, IL2RA, and CD58. This systematic collection of data can help to clarify the status of MS susceptibility genes and to prioritize future genetic studies.

- **Vitamin D and kids:** Beyond genes, other factors appear to play a role in the development of MS. Several studies focused on the potential influence of vitamin D levels and risk of MS. Researchers at two National MS Society-supported Pediatric MS Centers of Excellence (University of California at San Francisco and State University of New York, Stony Brook) retrospectively analyzed vitamin D blood serum levels in relation to relapse risk in 110 children with MS or CIS (having experienced a first neurological episode but not

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yet having confirmed MS). They found that low vitamin D3 levels were independently associated with the risk of relapse, after accounting for other factors such as age, gender, ethnicity, duration of MS and use of disease-modifying therapies. The authors report that every 10ng/ml increase in vitamin D levels was associated with a 34% decrease in relapse risk. The investigators appropriately suggest that a randomized, placebo-controlled, prospective study is needed to determine whether vitamin D supplementation improves the course of MS. (Abstract IN2-2.004)

- **Vitamin D, milk and mothers to be:** Fariba Mirzaei, MD, MPH, and colleagues at the Harvard School of Public Health used the ongoing Nurses Health studies to investigate levels of vitamin D intake – in the form of either milk or vitamin D supplements – of mothers whose daughters were enrolled in the nurse study. A questionnaire about their pregnancy with these daughters was completed by 35,794 mothers. MS was diagnosed in 199 of the nurses in the study. The investigators reported that the risk of developing MS among the daughters was significantly less if their mothers drank four or more glasses of milk per day, compared to mothers who drank less than three glasses of milk per month. Those whose mothers took larger amounts of vitamin D during pregnancy were also less likely to develop MS than those whose mothers took lower amounts. This study adds to growing evidence that vitamin D may reduce the risk of developing MS.

- **Vitamin D and immune cells:** How might vitamin D influence disease activity? Looking at one aspect of this question was a basic laboratory study by Edward Knapp, PhD, National MS Society Sylvia Lawry Physician Fellow Christopher Eckstein, MD, and Peter Calabresi, MD (Johns Hopkins University). Taking specific, active immune T cells (CD4+ T cells, which tend to drive MS immune attacks) from healthy participants, the team grew the cells in lab dishes for 72 hours with different concentrations of vitamin D. Then they sorted the cells and evaluated the types of messenger chemicals released by them. Compared to T cells that did not have vitamin D added, they found that vitamin D-treated cells released significantly less of the messenger chemicals interferon gamma and interleukin-17, both of which have been implicated in stimulating inflammation.

These and many other presentations reflect the rapid pace of MS research today.

With information from the National MS Society (USA)

National Research and Programs

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