

Medical Update Memo

Multiple sclerosis research progress prominent at ECTRIMS – ACTRIMS joint meeting September 28 – October 1, 2005

Advances in multiple sclerosis research were prominent at the 21st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held jointly with the 10th Annual Meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), September 28 – October 1, 2005, in Thessaloniki, Greece. This international meeting fosters collaboration and cross-pollination between basic and clinical MS researchers to propel the search for better therapies and a cure. Following is a selection of hundreds of presentations reporting progress in the fight against MS. The abstracts for all presentations are available online at www.akm.ch/ectrims2005

Clinical Trials

Disease-Modifying Drugs Delay Progression – Dr. P. Veugelers (University of Alberta, Edmonton) and colleagues collected data on 1,752 people with MS at the Dalhousie MS Research Unit between 1979 and 2004. They compared progression on the EDSS (a numerical scale that measures disease activity) in these patients before and after disease-modifying treatments (Avonex, Betaseron, Copaxone and Rebif) became available for MS. Before the availability of the therapies, the median time from disease onset to EDSS 4 was 10.4 years and to EDSS 6 was 14.5 years. After MS therapies became available, progression was delayed to 12.8 and 18.1 years respectively. In comparison, people who were eligible for treatment but had declined medication demonstrated the expected rate of progression. (EDSS 4: disability is present but the person is able to walk without mechan-

ical or human assistance: EDSS 6: person needs a single cane, crutch, or brace to walk).

Betaseron Delays Development of Definite MS – Professor Ludwig Kappos (University of Basel, Switzerland) and colleagues presented results from the BENEFIT study, which examined the ability of Betaseron® (interferon beta-1b, Berlex Inc.) to delay the onset of MS in people who experience a clinically isolated syndrome (CIS, a single demyelinating event, putting them at high risk to develop MS). A total of 487 patients received either Betaseron 250 mcg or placebo for up to 24 months or until MS was diagnosed. Twenty-eight percent of the Betaseron group had developed definite MS compared with 45% of the placebo group, and the development of MS was delayed by 363 days in the Betaseron group compared to the placebo group. A five-year follow-up study will assess the impact of early vs. delayed treatment on the long-term course of MS.

No Benefit – Dr. D. H. Miller (University College London, Queen Square, UK) and colleagues administered either Avandia® (rosiglitazone maleate, GlaxoSmithKline, Inc., a drug used to treat diabetes which affects hormones involved in the immune response) or placebo to 51 people with relapsing-remitting MS. No significant differences were found in tissue damage as detected on MRI, or in clinical or immunological responses to treatment. Treatment was well tolerated. The group found no evidence to support further studies of Avandia in MS.

Early-Stage Therapy Studies

Peptide Therapy Shows Promise – National MS Society-funded investigator Dr. A. Vandenberg and colleagues (Oregon Health Science University, Portland) reported on immunological analysis from a study of NeuroVax® (Immune Response Corporation) in people with relapsing and progressive MS. NeuroVax is a vaccine made of protein fragments from a docking site on the surface of T cells. By examining blood samples taken from six people before and after three monthly injections, investigators found that Treg cells - a type of T cell that can suppress the immune attack - were increased to a level equal to controls without MS. According to a company press release, in a subgroup of 12 people, there was a 15% decrease in the percentage of people with MRI scans showing active areas of myelin damage at 24 weeks.

T Cell Vaccination Reduces Immune Cells – Dr. B. Loftus and colleagues (Neurology Research and Diagnostic Clinic of Houston) conducted an open-label safety study using two

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doses of Tovaxin™ – T cell vaccination, an experimental therapy that induces immunity against T cells that attack nerve fibre-insulating myelin – to 15 people with relapsing-remitting or secondary-progressive MS. The treatment appeared safe, and T cells reacting to myelin were greatly reduced in all people in the higher dose group at five weeks after injection, and reductions were greater in this group than in the lower dose group at each of five follow-up visits. A larger study is planned.

Diagnosing/Tracking MS

Possible Diagnostic Marker – Dr. M. Freedman (University of Ottawa) and colleagues examined tissue from people who experienced a CIS, 44 of whom went on to develop MS and 44 of whom developed other neurological diseases. Levels of the immune system antibody GAGA4 IgM were significantly higher in people who eventually developed MS. Future studies will attempt to correlate such findings with MRI and determine whether this antibody might be used to diagnose and track MS using a simple blood test.

New Clue to MS-Like Disease – Dr. S. Pittock and colleagues (Mayo Clinic, Rochester, MN) recently discovered an antibody (an immune protein that attaches to and marks molecules for immune attack) in the blood of individuals with a disorder called neuromyelitis optica (NMO, also known as Devic's syndrome) that clearly distinguishes it from MS. NMO was until recently regarded as a severe form of MS. Now, they report finding areas of myelin damage in the brain tissue of 36 out of 60 people with NMO. The authors suggest revising the diagnostic criteria for NMO to include brain involvement. In recent, related news, this group identified the target of the antibody as a molecule called "aquaporin 4," a type of protein that allows for the passage of water (Journal of Experimental Medicine 2005 Aug 15;202(4):473-7.).

Genetics

Vitamin D and MS – Dr. G. Mamutse and colleagues (University Hospital of North Staffordshire Stoke on Trent, Staffordshire, UK) found that a variation in the gene for the vitamin D receptor, the docking site that determines how cells receive signals from vitamin D, was associated with reduced disability in a study of over 500 people with MS who had had MS for more than 10 years. Recent research indicates a possible link between vitamin D intake and a reduced risk of MS, possibly explaining lower rates of MS in areas of increased sunlight exposure, which results in increased production of vitamin D. Further studies are

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needed to confirm these findings.

Immune Genes – Dr. M. Bartolomé and colleagues (Hospital Universitario San Carlos, Madrid) found that the gene for early B cell factor, a molecule important in the development of immune B cells, was associated with the development of MS in people with another immune-related genetic variation. This provides further evidence for the role of B cells in the immune attack in MS.

Immunology

Altered Immune Regulation – Dr. A. Cross and colleagues (Washington University in St. Louis) report on a study of immune messenger proteins called "suppressors of cytokine signalling," or SOCS, which serve to regulate inflammatory immune messenger proteins. The group found that levels of SOCS-1 and SOCS-3 were lower in blood samples taken from people with MS than in those taken from control subjects without MS. Decreased amounts of these proteins may allow for the attack on the brain and spinal cord that occurs in MS.

MS & Pregnancy

Postpartum IVIG – Dr. J. Haas (Jewish Hospital, Berlin, Germany) reported on the Gammaglobulins Post Pregnancy in MS Study, a multicentre European study of IVIG (intravenous immunoglobulins, antibodies that may modulate the immune system). Investigators administered two different doses of IVIG to 163 women with relapsing-remitting MS within 24 hours after giving birth, and every four weeks thereafter for six months. The women were breastfeeding, and thus disease-modifying MS therapies were contraindicated. During the two years before pregnancy, the annual relapse rate among this group was 1, and the postpartum rate was similar or less. The results offer evidence of the effectiveness of IVIG during breastfeeding.

Pregnancy Outcomes – Dr. V. de las Heras (Hospital Universitario San Carlos, Madrid) reported final results from the EMPATIE Study on Pregnancy and MS Therapies, in which investigators reviewed 1,266 clinical records of 14 European centres since 1995 to identify women with MS who became pregnant after initiation of immunomodulatory therapy. Eighty-eight pregnancies were identified in 71 patients; 34.09% were unexpected and 65.91% were planned, with patients withdrawing from treatment prior to pregnancy. Spontaneous abortion occurred in 16.67% of those exposed to interferon beta (unplanned pregnancies) and in 22.41% of those not exposed (planned) – both comparable to the gener-

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al population. These results add to information on exposure to disease-modifying therapies during pregnancy.

Multiple Sclerosis Risk

Hepatitis B vaccination review – At a satellite symposium held prior to theECTRIMS-ACTRIMS meeting, a panel of international experts including Dr. Robert T. Naismith (UK), Prof. Christian Confavreux (France), Prof. Frauke Zipp (Germany) and Prof. Michel Lanet (France) reviewed the evidence that some say links hepatitis B vaccines to an increased risk for multiple sclerosis. Of eight studies that were reviewed in this presentation, seven showed no significant risk for people with MS. This includes a Canadian study by Dr. A. D. Sadovnik (University of British Columbia, Lancet 2000). Just one study found a link, and it has been criticized because only 6.7% of the study population with MS had received a hepatitis B vaccine. The Vaccine in MS study using the European Database for Multiple Sclerosis (EDMUS) showed that there is no increased risk of having a relapse following a hepatitis B vaccination in patients who were relapse free for the 12 months prior to vaccination. There was no evidence of increased disease activity on MRI following a hepatitis B vaccination.

ASK MS Information System Code: 2.8.2.q

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National Communications & Government Relations Department

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