NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Research Reports and Clinical Perspective

In this issue of CLINICAL NEUROLOGY NEWS, Neuroscience Today, Neurology Tomorrow focuses on potential therapies for multiple sclerosis. The studies described below evaluate two approaches to MS treatment that focus on axonal degeneration and vaccination-mediated immunosuppression. Prevention of disability in this chronic inflammatory disease remains the primary goal, and both approaches have demonstrated such efficacy in mouse models. But controversy persists regarding the comparability of experimental allergic encephalomyelitis (EAE) in an animal model and true multiple sclerosis in humans. And it is not clear whether therapies that are effective for murine EAE will in turn be effective for human MS. Nonetheless, they pave the way toward human clinical trials, the only forum in which efficacy really matters. Please send me your comments at clinicalneurologynews@elsevier.com.

BY RICHARD J. CASELLI, M.D.

Nicotinamide for MS?

Deficits in mice with induced multiple sclerosis–like autoimmune encephalomyelitis can be prevented or lessened after delayed treatment with subcutaneous injections of nicotinamide, the amide form of vitamin B_3 (niacin), reported Dr. Shinjiro Kaneko and his colleagues at Harvard Medical School.

Evidence suggests that the wallerian degeneration that is seen at the distal portion of transected axons is similar to the process of local axonal damage in MS and EAE. Based on that observation, the investigators studied whether mice that expressed the Wlds gene and had the slow wallerian degeneration phenotype could recover from chronic EAE. Wlds codes for an enzyme that is required for the biosynthesis of nicotinamide adenine dinucleotide (NAD).

Wlds mice had modest delays in the onset of behavioral deficits and attenuation of symptoms during the course of EAE, compared with control mice. Examination of spinal cord sections showed that axons in demyelinated areas were preserved in significantly greater numbers in Wlds mice than in controls, but no difference in the size of demyelinated areas was seen (J. Neurosci. 2006;26:9794-804).

Daily doses of 125 mg/kg or 500 mg/kg of nicotinamide (NAm) were given to both Wlds and control mice, starting on the day of EAE induction. On high-dose NAm, NAD levels remained elevated after 4 weeks in the Wlds mice but nearly normalized in control animals for an unknown reason. In controls, low-dose treatment produced results similar to Wlds expression alone, whereas high-dose treatment delayed the onset of disease and reduced the severity of behavioral deficits for at least 8 weeks. Wlds mice treated with high-dose NAm had the greatest level of protection. NAm reduced areas of T-cell infiltration and demyelination in both types of mice, unlike the effects of Wlds expression alone. A delay in high-dose NAm treatment until 10 days after EAE induction attenuated development of further EAE symptoms, prevented significant axonal loss, and modestly reduced inflammation and demyelination.

Dr. Caselli's comment: Can vitamin supplementation prevent MS relapses and slow the development of disability? Axonal loss, that may be progressive following an acute demyelination attack, results from inflammatory mediated axonal damage and contributes to disability in patients with MS. Some axons may be transected in this process and undergo wallerian degeneration. Many that remain physically connected still develop ovoidlike morphologic changes similar to those seen in wallerian degeneration. Previous research has disclosed the existence of a "slow wallerian degeneration" phenotype that results from overexpression of Wlds, a fusion protein. Wlds consists of nicotinamide mononucleotide adenylyltransferase 1 (NMNAT1, an enzyme required for NAD biosynthesis) and a short region of UFD2 (a ubiquitin assembly protein). Either inhibition of the ubiquitin-proteasome system or overexpression of Wlds (or NMNAT1) can slow wallerian degeneration. Kaneko and colleagues showed that transgenic mice expressing Wlds have less wallerian degeneration caused by EAE, and that nicotinamide (an NAD precursor) supplementation greatly reduces wallerian degeneration and improves behavioral deficits in EAE mice. Further, nicotinamide seemed to protect the mice from developing EAE. Dosage levels however were very high. Nonetheless, given the availability and safety profile of nicotinamide, therapeutic trials in MS may not be far away.

IL-17 Vaccination for MS

Active vaccination with an interleukin-17 complex designed to elicit an autoantibody response to the proinflammatory cytokine was effective in slowing the onset and reducing the severity of EAE in mice.

Till A. Röhn of Cytos Biotechnology AG, Zürich, and associates built an active vaccine by attaching a recombinantly expressed murine IL-17 to a viruslike particle from a bacteriophage, resulting in a highly ordered and repetitive display of antigens that was capable of inducing the production of antibodies against self-antigens without the need for adjuvants (Eur. J. Immunol. 2006 Oct. 18 [Epub doi:10.1002/eji.200636658]). IL-17 has been found in brain lesions and cerebrospinal fluid of MS patients.

Mice immunized with bacteriophage developed EAE 9 days after the disease was induced, whereas mice given the IL-17 vaccine developed EAE an average of 8 days later. The mice with the highest titers of anti–IL-17 antibodies during the initial phase of the disease did not show any signs of EAE until the end of the experiment. The vaccine significantly reduced EAE severity on average. Significantly fewer mice who received the vaccine reached the maximum severity score during the development of EAE, compared with control group mice (3 of 10 vs. 9 of 10).

In similar experiments, Dr. Catherine Uyttenhove and Dr. Jacques Van Snick of the Ludwig Institute for Cancer Research, Brussels, tested a vaccine composed of the IL-17A isoform conjugated to ovalbumin on mice who were induced to develop EAE after the last vaccine injection. Of 11 control mice, 9 had weight loss, floppy tails, and restricted mobility that began on day 12 after EAE induction and lasted until day 25. None of the vaccinated mice showed any disease (Eur. J. Immunol. 2006 Oct. 18 [Epub doi:10.1002/eji.200636662]).

Transient symptoms developed after EAE induction in 2 of 10 treated mice; 7 of 10 controls became disabled.

***Dr. Caselli's comment*:** Vaccination against IL-17 is a clever new approach to the therapy of chronic inflammatory diseases such as MS and rheumatoid arthritis, and its efficacy suggests that clinical trials may not be far off. Safety will be the main concern as IL-17–deficient mice have impaired neutrophil function and are known to be more susceptible to a variety of bacterial infections. In these studies, IL-17F remained active, and no infectious complications occurred, suggesting that IL-17F activity may be sufficient to maintain necessary immunoprotection while thwarting IL-17–mediated autoimmunity. One hopes that data from early phase clinical trials will show similar results that will then put infection-related safety concerns to rest. ■

Clinical perspective by DR. CASELLI, *chair of neurology at the Mayo Clinic, Scottsdale, Ariz., and professor of neurology at the Mayo Medical School, Rochester, Minn.*

Research reports by Jeff Evans, senior writer.

Experts Call for FDA Reform, Changes to Clinical Trial Design

BY MARY ELLEN SCHNEIDER
New York Bureau

BOSTON — Any proposals to reform the Food and Drug Administration should meet the test that the changes would have prevented the arthritis drug Vioxx from getting to the market, Dr. David J. Graham said at the annual meeting of the American Public Health Association.

Dr. Graham, an FDA scientist who testified before Congress in 2004 about the unwillingness of FDA officials to recognize safety problems with Vioxx (rofecoxib), was among a panel of experts who called for changes at the FDA and reforms in the way that pharmaceutical companies design clinical trials.

The FDA has been "captured" by the industry and has taken on the value system of the pharmaceutical companies, said Dr. Graham, of the FDA Office of Surveillance and Epidemiology, who was speaking as an individual and not on behalf of the agency.

FDA officials now see their jobs as getting drugs on the market as fast as possible, Dr. Graham said. "We have at FDA a lack of checks and balances."

FDA leadership was quick to rebut those charges. The vast majority of physicians, scientists, and staff members at the FDA reject the concept that the agency is beholden to the drug industry, Dr. Steven Galson, director of the Center for Drug Evaluation and Research (CDER), said in an interview.

In light of calls for reform, FDA officials have already taken a series of steps over the last 2 years to try to improve the processes within the agency, Dr. Galson said. But the biggest advances in drug safety are more likely to come from basic science advances, he said. These advances, which the FDA is trying to foster through its Critical Path Initiative, will help scientists better predict which drugs in development will run into safety problems later.

But the FDA also should improve its postmarketing surveillance, said panelist Dr. John D. Abramson, a clinical instructor in the department of ambulatory care and prevention at Harvard Medical School, Boston. The current system—in which physicians voluntarily report drug-related adverse events—does not work, because it's passive, he said. The FDA could instead be doing epidemiologic studies to monitor side effects in the entire population taking a drug.

Drug companies used to simply provide financial support for studies, but they now also design the study and keep the research, said panelist Dr. Marcia Angell, former editor-in-chief of the New England Journal of Medicine and a senior lecturer on social medicine at Harvard.

One possible way to limit the influence of pharmaceutical companies in study design would be to create an arm of the National Institutes of Health that would oversee the design of trials, Dr. Angell said, adding that such a body could be wholly or partially funded by industry. Registration of clinical trials at their inception should be a requirement to enroll human subjects, she added.

The panel also criticized the FDA statute that requires new drugs to show effectiveness compared with placebo, but does not require a new drug to be better than existing medications on the market. This leads to approval of drugs with limited benefits and unknown risks, Dr. Angell said. ■