

# MS

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## B CELLS: AN EMERGING TARGET FOR MS THERAPY

**A**lthough the exact cause of multiple sclerosis (MS) remains elusive, the prevailing theory is that an autoimmune attack against the myelin sheath and axons plays an important role. Most research on the pathogenesis of MS has focused on T cells, which coordinate much of the immune response. However, investigators are increasingly turning their attention to another main component of the immune system: B cells. Best known for their ability to become antibody-producing plasma cells, B cells may play an underappreciated role in the MS disease process—and might offer researchers new targets for therapy.

“Although the data are not as strong as the data we have for T cells, I think that we’ll definitely find that B cells are participants in the pathology of MS, at least for a subset of patients,” noted Kevin O’Connor, PhD,

an Instructor in Neurology at Harvard Medical School and Brigham and Women’s Hospital in Boston.

Several lines of evidence implicate B cells in the development of MS. For example, the majority of persons with MS have elevated levels of immunoglobulins in their cerebrospinal fluid (CSF), including oligoclonal antibodies, which indicate that B cells have been activated, have undergone clonal expansion, and have begun churning out large quantities of antibodies. At least two thirds of MS patients have CSF antibodies to myelin. Moreover, biopsy samples from MS lesions contain deposits of antibodies against myelin proteins around damaged myelin sheaths as well as in macrophages, the cells that engulf debris from damaged cells.

Recent evidence suggests that a B cell’s role may not end there. “People have always thought that impli-

cating B cells must also mean implicating plasma cells and antibodies,” noted Amit Bar-Or, MD, Assistant Professor of Neurology and Neurosurgery at Montreal Neurological Institute and McGill University in Montreal. “Now, it looks as though B cells are involved in several other aspects of the normal immune response, including presenting antigen to T cells, regulating the immune response by producing cytokines, and contributing to the formation of the architecture of lymph nodes. A dysregulation of one or more of these functions contributes to an abnormal state [such as MS], independent of antibodies.”

None of this necessarily means that abnormalities in B cells are sufficient to cause the disease, Dr. Bar-Or suggested. It may be that B cells become involved only after some initial damage to the nervous system.

“One fact that makes this an ap-

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peeling theory is that the myelin antigens are well protected,” added Dr. O’Connor. “They’re not well-exposed unless there’s damage. So perhaps it’s only after the damage has started to occur—whether through spontaneous degeneration or T-cell induced injury—that B cells play a role in pathogenesis.” Also, investigators have not yet completely ruled out the possibility that the antibody response in MS is merely an epiphenomenon—that plasma cells dutifully produce antibodies to fragments of myelin but have little or no direct impact on the disease itself.

### PROMISE FOR PROGNOSIS

In all likelihood, the role of B cells varies in the different MS subtypes, suggested Claude Genain, MD, Associate Professor of Neurology at the University of California-San Francisco. “At one end of the spectrum are diseases like neuromyelitis optica—an MS-like condition characterized by transverse neuromyelitis and optic neuritis—which clearly appears to be heavily mediated by B cells, antibodies, and complement. At the other end, there are forms that are probably mediated more by T-cell immunity. The implication is that when we better understand these diseases, we will be able to treat patients according to their disease mechanisms. Some patients will benefit from therapies that suppress B cells while others will respond better to interferon, which acts primarily on T cells.”

A recent study from the Mayo Clinic provided an illustration of how patients may benefit from matching therapies to particular disease mechanisms.<sup>1</sup> The investigators used plasma exchange to treat 19 patients with early active MS who had not responded to cortico-

steroids. All 10 of the patients whose lesions had substantial antibody deposition and complement activation showed moderate or greater improvements in neurologic function following treatment. However, no meaningful improvement occurred in any of the nine patients whose lesions lacked antibody deposits.

Similarly, a patient’s antibody status may one day help clinicians provide a more accurate prognosis. Some evidence suggests that patients whose CSF contains few or no oligoclonal bands are more likely to have relatively benign disease. In 2003, a team of

Might therapies that suppress B cells help keep the disease at bay? “Evidence from both experimental animal models and emerging human studies supports this contention very strongly,” said Dr. Genain.

German researchers reported in the *New England Journal of Medicine* that patients who presented with clinically isolated syndrome had a substantially increased risk of subsequent episodes if they had serum antibodies to myelin proteins such as myelin oligodendrocyte glycoprotein (MOG) and myelin ba-

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## Table

### SELECTED MS THERAPIES THAT ALTER B-CELL FUNCTION

Mitoxantrone	Suppresses the proliferation and function of B cells, T cells, and macrophages. Approved for treatment of worsening MS.
Rituximab	Monoclonal antibody that binds to the B-cell antigen CD20. Approved for the treatment of non-Hodgkin's lymphoma; being tested in trials for MS.
Natalizumab	Monoclonal antibody that binds to surface of all leukocytes, including B cells, thereby disrupting transmigration into inflamed tissue. Approved for the treatment of MS in 2004 but withdrawn by its manufacturer in 2005 due to safety concerns.
Alemtuzumab	Monoclonal antibody that binds to CD52, an antigen on B cells, T cells, and macrophages. Approved for treatment of B-cell chronic lymphocytic leukemia; being tested in MS trials.
FTY720	Monoclonal antibody that binds to T and B cells. Phase III trial in MS scheduled to be launched in late 2005.
Cyclophosphamide, Corticosteroids	Suppress B cells and T cells; often used to treat MS exacerbations.
Plasma exchange	Removes antibodies and complement from blood.

sic protein (MBP).<sup>2</sup> More recently, researchers reported that, in another series of patients, no evidence was found that the presence of anti-MOG or anti-MBP antibodies in the serum facilitated earlier diagnosis of MS.<sup>3</sup> Nonetheless, the prospect that “we can use serum antibody markers as predictors of patients’ future disease process is very exciting,” Dr. Genain said.

#### TRIALS AND TRIBULATIONS

If B cells do, in fact, play a meaningful role in MS, might therapies that suppress these cells help keep the disease at bay? “Evidence from both experimental animal models and some emerging human studies supports this contention very strongly,” according to Dr. Genain. Of the current FDA-approved medications for MS, neither glatiramer acetate nor the interferon beta regimens have a substantial impact on B cells. However, mitoxantrone suppresses the proliferation and function of T cells and macrophages as well as B cells, thus inhibiting such processes as antibody production and antigen presentation. Similarly, some of the older immunosuppressants that are commonly used to treat MS exacerbations appear to have effects on both T and B cells (Table).

A new breed of therapies that specifically target B cells is beginning to emerge. One of these drugs, ritux-

imab (Rituxan<sup>®</sup>) is now being studied in at least three clinical trials. Approved in 1997 for the treatment of non-Hodgkin’s lymphoma, rituximab is a monoclonal antibody that targets CD20, a protein that regulates mitosis and differentiation of B cells. The drug is currently being tested in a 61-site, two-year, Phase II/III trial in 435 people with primary progressive MS, for which no therapies are currently FDA-approved. The primary outcome measure is time to confirmed disease progression. Outcome data are expected within three years, according to Kathleen Hawker, MD, a principal investigator for the study.

Two additional rituximab trials are being conducted in patients with relapsing-remitting disease. The 180-patient HERMES trial was launched in December 2004; the main outcome measure is lesions

on MRI. Also, researchers at Washington University in St. Louis are examining whether rituximab is beneficial as add-on therapy to interferon beta or glatiramer acetate. Initial analyses of patients’ CSF in this small study revealed reductions of about 70% in B cells and 33% in IgG synthesis, lead author Anne H. Cross, MD, reported at last spring’s annual meeting of the Consortium of Multiple Sclerosis Centers.

In addition, a recent study published in *Neurology* involving eight patients with worsening neuromyelitis optica supported the role of rituximab in achieving B cell depletion: six of the eight participants were relapse-free through a two-year follow-up period after receiving IV rituximab.<sup>4</sup>

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—Peter Doskoch

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# MS CLINICAL TRIALS FOCUS ON NEW AGENTS, INNOVATIVE APPROACHES



Although existing disease-modifying agents have dramatically changed the treatment approach to multiple sclerosis (MS), these agents are not effective in all patients or fully capable of suppressing disease activity. In an effort to make more inroads against this disease, researchers have set their sights on widely differing approaches—from monoclonal antibodies to new combinations of current MS therapies.

The most promising of these approaches involves the identification and evaluation of highly targeted antibodies. More than a dozen such studies are in progress and researchers are on a fast track to launch others.

## TARGETING ANTIBODIES

“In the last two years, we’ve gained much knowledge of the potential utility of monoclonal antibodies for treating patients with MS. The challenge has been finding the appropriate target,” said Walter Royal, III, MD, Associate Professor of Neurology at the University of Maryland School of Medicine in Baltimore and Associate Research Director for the Baltimore Veterans Affairs MS Center of Excellence. “Some of the targets have been relatively specific, though in some cases not specific enough to avoid complications. For example, an antibody may deplete an immune cell type that might be as much protective as it is toxic or detrimental to patients with MS.” The goal, he explained, is to more selectively target cell subsets that are involved in the immune system attack without disturbing those that are not involved.

The monoclonal antibodies currently attracting the most research attention are daclizumab (see sidebar), alemtuzumab (Campath®), and natalizumab (Tysabri®). In a Phase III study of alemtuzumab, the drug decreased relapses by 75% compared with interferon beta-1a (Rebif®), noted James Bowen, MD, Associate Professor of Neurology at the University of Washington in Seattle. However, since a small number of patients developed immune thrombocytopenic purpura (with one recorded fatality), the study is now on hold.

Results of the Phase III SENTINEL (Safety and Efficacy of Antegren in Combination With Interferon beta-1a in Subjects With Relapsing-Remitting MS) study were reported during the recent 21st Congress of the European

Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Greece. As combination therapy with Avonex®, natalizumab significantly reduced active brain lesions in 1,171 patients.

In February 2005, Biogen Idec and the Elan Corporation voluntarily suspended natalizumab from the market and from clinical trials based on three reports of progressive multifocal leukoencephalopathy (PML), two of which were fatal, in clinical trial participants. However, recent findings from safety evaluations of natalizumab in MS (1,800 patients) and Crohn’s disease/rheumatoid arthritis (1,300 patients) revealed no new confirmed cases of PML. On September 26, the companies announced that they had submitted a supplemental Biologics License Application (sBLA) for natalizumab to the FDA with priority review status and would resume clinical trials. If granted, the sBLA would result in FDA action within six months of submission date.

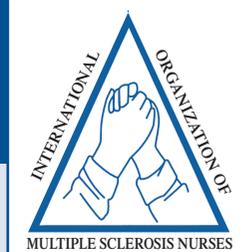
## COMBINING THERAPIES

Interest in combination therapies has increased substantially in recent years. Most studies in this area involve add-on therapies to existing disease-modifying treatments, noted Dr. Bowen. Drugs combined with these

The goal [in monoclonal antibody therapy] is to more selectively target cell subsets that are involved in the immune system attack without disturbing those that are not involved.

agents include corticosteroids, bronchodilators such as albuterol, intravenous immunoglobulin, mycophenolate, and methotrexate.

“Most of these are really Phase I studies with no control groups,” Dr. Bowen explained. However, he pointed to the CombiRx trial as one that warrants the MS community’s attention. This is a multicenter, randomized, double-blind, placebo-controlled study of glatiramer acetate or interferon beta-1a alone or in combination in patients with relapsing-remitting MS. The three-year study will consist of three treatment arms: interferon beta-1a IM and glatiramer acetate SC (50% of patients); interferon beta-1a



## Multiple Sclerosis Nursing in 2005: A Global Perspective

### Psychosocial Issues in MS

In addition to the profound physical impact of the disease, multiple sclerosis (MS) has a significant psychosocial impact that encompasses all areas of life. In particular, depression affects up to 50% of patients with MS.<sup>1</sup> Besides being aware of mood disorders in this population, clinicians should also know the definable points during the course of MS when the psychosocial impact of the disease may be heightened, according to Cathy-Lee Benbow, MSW, RSW.

“Those with MS must live with constant uncertainty, loss of control, change in self-image, and grief over real or anticipated loss,” explained Ms. Benbow, of the MS Clinic of London Health Sciences Centre, Ontario, in an interview with *MS Exchange*.

### Assessment Is Key

According to Ms. Benbow, an MS patient’s psychosocial status should be assessed prediagnosis (when the person has had one neurologic event but cannot be definitively diagnosed with MS), upon diagnosis, during exacerbations, and with continued disease progression. People with a history of mood disorders such as depression or panic attacks may be particularly vulnerable during these times.

Assessment should include family history of mood disorders, history of suicidal thoughts or attempts, his-

tory of addiction or alcohol/substance abuse, and history of anxiety disorders. Current situational stressors and real or anticipated losses, such as the ability to work or drive, should also be taken into account.

It may be beneficial to query the patient about how he or she has handled grief, loss, and/or uncertainty in the past. “If an individual relates a history of maladaptive coping mechanisms, that’s certainly a red flag,” Ms. Benbow added.

### Facing Uncertainty and Loss of Control

“As I tell patients with MS: Uncertainty is now your partner,” said Ms. Benbow. “This is true even if they never have another neurologic symptom or change on MRI.” For some people, this lack of knowledge about what the future holds can be immobilizing. To help patients deal with this fact of life with MS, Ms. Benbow asks them how they have dealt with uncertainty during other challenging periods of their lives. Patients can then use these experiences as a guide for what to do—or not do—in other situations where answers aren’t readily apparent.

Loss of control is another stumbling block to many with MS. Patients may question clinicians about how to prevent the development of MS, how they can keep the disease from progressing, and how they can make ex-

acerbation periods pass more quickly. “We need to gently explain to these patients that, although we can’t completely stop the disease from developing or progressing, we can help people control how they adapt to the changes MS will bring to their lives,” advised Ms. Benbow.

### Depression in MS

The physical manifestations of MS bring loss in all areas of patients’ lives. Although brain lesions may be associated with depression,<sup>2</sup> the onset of a mood disorder may result from real or anticipated loss. “The patients I see often can’t do the things they once could—be it working, socializing, or driving,” said Ms. Benbow. “They may respond to such life-altering changes by becoming depressed.”

Drugs used to treat MS—particularly the interferons—have been linked to increased risk for depression.<sup>3</sup> However, whether these or any drugs directly cause mood disturbance in MS patients is very hard to determine, since many other situational factors may contribute to depression, Ms. Benbow explained.

Asking how the person recognized depression in the past may help him or her to identify “danger signs” in the future. Then, the clinician and the patient may be able to put a tentative plan in place—such as a referral to a mental health counselor—should the person begin to feel emotionally overwhelmed again.

## Helping Patients Cope

“For most of us, it’s hard to find time to initiate a discussion on mood disorders with our patients,” said Ms. Benbow. “However, we need to be aware of their prevalence within this population and be able to develop systems to handle assessment and treatment.” Having contact information on hand for therapists familiar with working with people with MS is a valuable resource.

It’s also critical to remind patients that their attitudes need to change along with their health status. “A lot of patients get stuck on what they can’t do. It’s our job to help them focus on what they’re still able to accomplish, and to help them find new ways of doing things,” Ms. Benbow stated. People with MS should be encouraged to redefine who they are now that they are living with this illness, and to see that they are still worthwhile and productive.

“All health care providers have a huge role in helping MS patients to adapt to their illness. We can make a real difference in the emotional well-being of these individuals,” stressed Ms. Benbow. “Although none of us can help patients live without MS, we all can help them to live better with it.”

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—Krista Binetti

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## Pharmacologic Management in MS

### The Role of the APN

In collaboration with a physician, many advanced practice nurses (APNs) in the field of multiple sclerosis (MS) can diagnose symptoms and diseases and prescribe drugs to patients under their scope of practice. At the recent IOMSN-sponsored conference, “Update for Advanced Practice Nurses,” held August 12–14 in Laguna Niguel, California, Heidi Maloni, APRN, BC-ANP, CNRN, MSCN, discussed the role of the APN in the pharmacologic management of MS.

“Nurses are professionally, legally, morally, and personally responsible for every dose of medication they pre-

scribe,” Ms. Maloni stressed. “Therefore, it’s imperative that the MS nurse in advanced practice know how to safely administer pharmacologic agents.”

## Safety Measures

In order to prescribe drugs safely, the APN must gather basic health and psychosocial information on each patient. “For example, it’s important to know if a patient is pregnant or is planning a pregnancy, as some drugs are contraindicated or to be used with caution in such individuals,” Ms. Maloni stated. Certain drug precautions also apply to males trying to conceive, as some drugs commonly prescribed in MS, such as corticosteroids or antiepileptics, decrease sperm motility.

A psychosocial history that includes education level, social support, and personal habits is another critical component of the APN’s assessment.

Taking a thorough medication history is also important, as it may help in the development of strategies to improve adherence. A psychosocial history that includes education level, social support, and personal habits is another critical component of the APN’s assessment. For example, some patients may have trouble reading and understanding their medication directions or medical literature on available therapies. Asking patients to bring in their current medications and describe their use helps the APN to determine each patient’s comprehension level.

Patients may be reluctant to discuss OTC or alternative/herbal medications that they are taking. However, “the APN should inquire whether the patient is using any of these medications, as well as any recreational drugs,” Ms. Maloni advised. Individuals should be cautioned that prescribed drugs may interact with OTC agents and alternative/herbal preparations, and that some “natural” remedies have been shown to exacerbate MS symptoms.

## Testing Liver Function

Recent medical literature has documented the occurrence of liver toxicity with the use of the interferons.<sup>1,2</sup> “As clinicians, we wonder why adverse effects occur and ask how

we can prevent them while preserving beneficial effects," stated Ms. Maloni. To achieve this goal, APNs must know each drug's pharmacodynamics and mechanism of action.

"One of our goals as MS nurses is to help our patients stay on immunomodulating therapy," she said. In the event of an abnormal liver function test in an MS patient, Ms. Maloni advised against immediately discontinuing any one drug. "Instead, the test should be repeated, a CPK enzyme test should be ordered, and an alcohol history should be taken before an abnormal test is attributed to medication-induced causes," she explained.

### Minimizing Drug Interactions

To help minimize interactions, it's important for nurses to keep in mind all of the drugs a patient is taking, and to know the difference between drug inducers and drug inhibitors. "Inducers are drugs that are added to a medication regimen and decrease the therapeutic levels of the main drug," explained Ms. Maloni. For example, a person who has been taking modafinil for MS-related fatigue and is then prescribed carbamazepine for seizures and/or pain will likely experience a decrease of the therapeutic effects of modafinil. On the opposite end of the spectrum, if the main drug (or substrate) being used is an oral contraceptive (OC), a drug such as ketoconazole—often prescribed to treat a yeast infection—may act as an inhibitor and decrease the therapeutic effect of the OC. Some drugs, such as glatiramer acetate, have few or no interactions with other agents.

People metabolize and eliminate drugs at different rates, which are dependent on variables such as age, weight, height, gender, and, particularly, ethnicity. As a result, it's important for the APN to conduct a thorough cultural assessment of each patient, Ms. Maloni stated. "For example, many people from a Middle Eastern background are slow metabolizers of CYP2D6 agents, such as antidepressants. Therefore, these drugs may seem 'stronger' in this population," she explained. In contrast, Asians may have a higher metabolism for opiates than do Caucasians; as a result, their dosages of these types of drugs may need to be raised for an appropriate therapeutic effect.

Patients should also be asked specific questions about side effects they've experienced from medications taken in the past.

"Unfortunately, in our busy practices, it is a challenge to manage our patients' medication regimens," Ms. Maloni admitted. "Knowing about drug pharmacokinetics and pharmacodynamics will guide the APN

in making treatment decisions that work for each individual patient and help all of our MS patients to have a better quality of life. APNs have the knowledge and skills to meet the challenge," Ms. Maloni stated.

For more information on this topic, please e-mail Heidi Maloni at [Maloni@cua.edu](mailto:Maloni@cua.edu). Slides from Ms. Maloni's presentation may also be found on [www.iomsn.org](http://www.iomsn.org). **MSX**

—Krista Binetti

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## IOMSN Nurse Mentorship Program: A Successful First Year

Launched in early 2005, the IOMSN-sponsored Nurse Mentorship Program has already become an overwhelming success. The program is an educational opportunity for nurses to become familiar with the skills and knowledge necessary to provide patients with the highest quality of specialized MS nursing care.

"The program is getting extremely positive feedback," stated Colleen Harris, RN, NP, Chair of the Educational Committee of the IOMSN and member of the Mentorship Committee. "We now have 30 mentors across the United States who are working with apprentice nurses." Although

### INTERESTED IN SHARING YOUR KNOWLEDGE WITH THE WORLD? JOIN THE IOMSN!

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most apprentices in the program are new to MS, some were already working in the field and entered the program to gain from the knowledge of a more experienced MS nurse, explained Ms. Harris.

One important benefit for apprentice nurses is the opportunity to be introduced to the large MS nursing support network and its resources, according to Amy Perrin Ross, APRN, MSN, CNRN, MSCN of Loyola University Medical Center in Maywood, Ill. Ms. Perrin Ross is also on the Mentorship Committee and has served as a mentor since the program's inception.

"We try to match each nurse with the most appropriate mentor," explained Ms. Perrin Ross. "We also do our best to honor requests for specific mentors, such as those whom apprentices have met or heard speak at MS conferences."

Ms. Perrin Ross begins each mentoring experience by assessing what the apprentice most wants to achieve during the program's duration. "For example, some might want to watch an NP do a full neurologic exam, while other apprentices might be more interested in learning about our MS center's approach to progressive disease. Still others may want to learn how we manage side effects and make treatment decisions with patients."

Ms. Perrin Ross also tries not to schedule many patients on days she is mentoring, to allow for time to discuss patients' cases. "I may also talk with patients on speakerphone, with their permission, so that the apprentice can learn about the types of calls we get from patients and how to determine when phone counseling is warranted versus an office visit."

Through her mentoring experience, Ms. Perrin Ross

has learned valuable information about her own nursing style. "Explaining my treatment decisions to the apprentice helps me to become more aware of why I'm making these decisions," she related. Patients have also found the experience rewarding, as they have been in the presence of nurses having open discussions on such issues as symptom and side effect management.

Added Ms. Harris, "We hope to be able to use this model for other IOMSN-sponsored programs in the future, including, possibly, an international version of the Mentorship Program."

To be eligible for the program, an apprentice applicant must have an RN license, or approved equivalent from another country, and at least 12 months of clinical nursing experience. After being matched with an appropriate mentor and completing the two-day mentorship program, each apprentice should be able to identify aspects of comprehensive MS nursing care; become an active participant in the MS clinical community; and describe future learning needs for other educational opportunities. Nurses who complete the program may be eligible to sit for the MS Nursing Certification Exam and are entitled to funding to cover the registration fee.

Applications for the Nurse Mentorship Program are currently being accepted for 2006. Nurses who wish to become mentors or apprentices in this program may contact the IOMSN by e-mail at [info@iomsn.org](mailto:info@iomsn.org). All candidates may obtain more information and download applications from the IOMSN Web site at [www.iomsn.org](http://www.iomsn.org). **MSX**

—Krista Binetti

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## NEWLY LAUNCHED MONOCLONAL ANTIBODY STUDIES IN MS

### ABT-874 (anti-IL-12 antibody)

This investigational drug is a fully human anti-interleukin-12 (IL-12) monoclonal antibody. IL-12 is a protein that regulates inflammatory response and is associated with several chronic inflammatory autoimmune disorders, including MS and Crohn's disease. Studies of anti-IL-12 antibodies in animal models have demonstrated inhibition of demyelination, noted Elliot Chartash, MD, global project head for Abbott Laboratories, the drug's developer. Based on those findings, Dr. Chartash said, ABT-874 is now being studied in a global, 120-week, placebo-controlled, Phase II trial that will evaluate its safety and efficacy in reducing brain lesions.

### CHOICE Study (daclizumab)

CHOICE is a Phase II, multicenter, international trial involving the first approved humanized monoclonal antibody, daclizumab, which is currently used in organ-transplant patients. Earlier trials sponsored by the National Institutes of Health found this antibody to be effective in reducing new contrast-enhancing lesions in MS. The CHOICE trial, which seeks to enroll 270 patients with active, relapsing MS, will compare the effectiveness of high- and low-dose daclizumab versus placebo in reducing the mean number of total and new contrast-enhancing lesions. The agent is thought to target the critical IL-2 receptor, important in T-cell proliferation. At the same time, it does not "shut down or deplete the critical arms of the immune response—as with traditional immunosuppressive agents used to treat MS," said one of the trial's principal investigators, Daniel Wynn, MD, Director of Clinical Research and Co-Director of the Consultants in Neurology Multiple Sclerosis Center in Northbrook, Ill.

IM and placebo SC (25%); and glatiramer acetate SC and placebo IM (25%). The primary outcome measure for this study is effect on annualized relapse rate.

### OLD DRUGS, NEW USES?

The use of statins has also emerged in recent MS trials. The largest of these is a randomized, double-blind, placebo-controlled, multicenter study of the cholesterol-lowering drug atorvastatin (Lipitor®) in 152 patients with clinically isolated syndrome (CIS). In previous studies, atorvastatin was shown to prevent or reverse experimental autoimmune encephalomyelitis,

suggesting that it may also alter immune response in MS.

Patients will be randomly assigned to receive either 80 mg atorvastatin or placebo orally once daily for 12 months. Participants must have received a three- to five-day course of IV corticosteroids within 60 days of onset and at least 28 days before the start of the study. A team of researchers led by Scott Zamvil, MD, PhD, Associate Professor of Neurology at the University of California—San Francisco Multiple Sclerosis Center will gauge the ability of the drug to decrease or delay clinical and MRI disease activity in CIS patients. The trial is scheduled to last for 18 months.

### INDUCING REMYELINATION

One innovative approach being considered for MS treatment is the use of mechanisms to induce remyelination. A number of such approaches are being studied including various growth factors, types of immune reactions that promote remyelination, and stem cell transplants. "Most trials in this area to date have been limited to animal models," Dr. Bowen explained. One such trial, involving autologous bone-marrow derived stem cell transplants in mice, is now being carried out by investigators at the University of Maryland School of Medicine. "There have been some small studies in humans utilizing stem cell transplants," said Dr. Bowen. "However, for all practical purposes, this work is still in the preclinical phase of development."

### THE PROMISE OF THE FUTURE

Despite the early stage of these novel treatment approaches in MS, progress in recent years has been considerable—and the developments herald a promising new chapter in MS treatment, Dr. Royal noted. He added that his institution is conducting a newly launched (non-treatment) pilot study to evaluate the potential effects of vitamin D supplementation on immune function in patients with MS. The university is also a site for the CombiRx trial as well as a recently launched trial of the monoclonal antibody rituximab, currently being used with good results to treat non-Hodgkin's lymphoma, in relapsing-remitting MS.

"In general, the new therapies are reflecting more innovation and greater specificity. The hope is that, over time, these drugs will become even safer and that they will yield longer-lasting effects associated with nervous system repair," Dr. Royal said. "I think we're starting to see therapies move in that direction." **MSX**

—Bonnie Daroes

## LITERATURE MONITOR/ NEWS ROUNDUP



### STUDY SHOWS ORAL CONTRACEPTIVE USE MAY DELAY FIRST MS SYMPTOMS

Women who use oral contraceptives (OCs) may be temporarily staving off the initial onset of MS, according to results of a recently published case-control study from the Harvard School of Public Health and other centers.

Using a database of over three million British patients (the General Practice Research Database), the investigators selected 106 cases involving women under 50 with definite MS who had their first symptoms during the period of data recording and for whom at least three years of continuous information was available. OC use and pregnancy history in these women were compared with those of 1,001 age-matched female controls in the database.

Of the 106 women with MS, 52.8% were current or former users of OCs, as were 60% of control subjects. The incidence of MS was 40% lower in women using OCs than in nonusers (OR, 0.6; 95% CI, 0.4–1.0). Duration of OC use and time since last use were not definitively correlated with MS incidence, but the authors suggested that the highest reduction in risk appeared to be associated with more recent OC use. In contrast, risk for developing MS increased in the six months following pregnancy, a finding consistent with other studies of pregnancy and MS.

According to the authors, these results support the theory that estrogen—either exogenous from OCs or endogenous from pregnancy—confers some protective effect that may delay the first clinical attack of MS.

Alonso A, Jick SS, Olek MJ, et al. Recent use of oral contraceptives and the risk of multiple sclerosis. *Arch Neurol.* 2005;62:1362-1365.

### PUTTING THE STING ON MS, OR JUST A LOT OF BUZZ?

Bee venom therapy is an alternative MS treatment attracting a lot of buzz—but does it do any good? To find out, a group of investigators from the Netherlands designed a medically supervised, randomized, open, crossover trial comparing bee-sting treatment with no treatment in patients with relapsing-remitting or secondary progressive MS.

Interestingly, 113 patients volunteered to be stung by bees for the study. Twenty-six met eligibility requirements, which included clinically definite MS, Expanded Disability Status Scale score less than or equal to 6.5, and

either recently documented relapse and/or MRI evidence of progression. Those at risk for anaphylactic reaction were ineligible. Patients were divided into two groups, to receive either bee stings or no therapy for 24 weeks. The two groups were then switched for an additional 24 weeks. Bee stings were administered on the upper legs three times per week, with an incremental increase of one sting per session (maximum of 20 stings per session).

All participants underwent gadolinium-enhanced MRI scans at baseline and every six weeks during the trial period. The primary outcome measure, cumulative number of new gadolinium-enhancing lesions on T1-weighted MRI, “has been shown to be a reliable tool for short-term exploratory trials of new interventions,” the authors noted.

The investigators found that bee venom therapy had no significant effect on disease activity in this trial. Adverse effects included swelling, local tenderness, redness, and itching. One patient refused to stop the therapy and arranged for continued treatment through a beekeeper.

Bee venom is believed to have anti-inflammatory properties and contains a polypeptide called apamin, which may play a role in regulating neuronal activity. However, these results from one of the few controlled trials of bee venom in MS suggest that patients stay away from bee hives and stick with more established therapies.

Wesselius T, Heersema DJ, Mostert JP, et al. A randomized crossover study of bee sting therapy for multiple sclerosis. *Neurology.* 2005;65 [E-pub ahead of print].

### NURSING HOME STUDY LOOKS AT IMPACT OF DEMENTIA IN MS

Despite increasing research, cognitive impairment in MS remains challenging to evaluate and treat on many lev-

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els. Dementia in MS patients can be particularly difficult, as little research exists to elucidate its causes or to differentiate it from other forms of cognitive impairment.

A group of researchers from Mississippi and Texas focused on nursing home residents with MS to determine how those with dementia differed from those with normal cognition. Using data from the Minimum Data Set, a federally mandated nursing home assessment instrument, they identified 20,561 residents with a diagnosis of MS upon admission to a nursing facility between January 1998 and June 2003 and 2,235 residents who had both MS and dementia, including Alzheimer's and non-Alzheimer's types. The following were compared in the two populations: demographics; measures of cognitive ability, physical impairment, mood, and behavior; comorbidities; and therapies.

A number of significant differences were observed between MS patients in nursing homes with and without dementia. Those with dementia were older (mean age 65.4 at admission, vs 55.7 for those without dementia) and less likely to have physical disabilities limiting their activities of daily living. Nearly two thirds of residents with dementia had moderate or severe cognitive impairment, while those without dementia were more likely to be cognitively intact and responsible for making decisions about their care. Depression was significantly more prevalent and more difficult to treat in the population with dementia. Pain was reported more often in the group without dementia, while cardiovascular complications such as stroke or congestive heart failure were more common in the group with dementia.

Newer MRI methods have suggested an association between frontal lobe dementia in MS and a greater total and frontal lobe lesion burden, the authors noted. However, this should also correspond with an increase in other neurologic deficits such as weakness, sensory loss, and ataxia, which was not found in this study.

Buchanan RJ, Martin RA, Moore L, et al. Nursing home residents with multiple sclerosis and dementia compared to other multiple sclerosis residents. *Mult Scler.* 2005;11:610-616.

## ENERGY CONSERVATION COURSE REDUCES FATIGUE IMPACT

Courses that teach people with MS how to conserve their energy and reduce fatigue may sound like a good

idea in theory, but until recently such programs had little data to back up their effectiveness.

The May 2005 issue of *MS Exchange* reported on a trial by Virgil Mathiowetz, PhD and colleagues that tested the efficacy of an energy conservation course designed by Packer et al in people with MS. Recently published in the journal *Multiple Sclerosis*, the results show that the course decreased fatigue impact and increased some quality of life measures in 169 MS patients.

Participants with moderate to severe fatigue were randomly assigned to two groups. One group participated in a six-week energy conservation course immediately, and the other group received the course after an initial six-week, no-intervention, control period. The Fatigue Impact Scale (FIS) was used to quantify changes in patients' experience of fatigue, while a standard research tool (the SF-36 Health Survey) was used to evaluate perceived quality of life measures.

A secondary outcome measure was self-efficacy for performing energy conservation strategies. This was assessed using the the Self-Efficacy Gauge; participants used a 1 to 10 scale to identify their level of confidence in performing the strategies taught during the course.

The six sessions in the energy conservation program taught concepts such as the importance of rest throughout the day; positive and effective communication; proper body mechanics and ergonomic principles; setting priorities; and living a balanced lifestyle. The results showed a statistically significant improvement on the physical, social, and cognitive subscales of the FIS, and on the vitality, role-physical, and mental health subscales of the SF-36 for patients receiving energy conservation training.

The investigators noted that part of the program's success may stem from its group format and the active learning activities employed during the course. "When participants were not successful, other participants often challenged them to adjust their standards and to try new strategies," they wrote. **MSX**

Mathiowetz VG, Finlayson ML, Matuska KM, et al. Randomized controlled trial of an energy conservation course for persons with multiple sclerosis. *Mult Scler.* 2005;11:592-601.

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Subscription inquiries should be directed to *MS Exchange*, Jobson Medical Group, 1515 Broad Street, Bloomfield, NJ 07003; telephone (973) 954-9300; fax (973) 954-9306. MSE0504. All editorial correspondence should be sent to *MS Exchange*, Jobson Medical Group, 1515 Broad Street, Bloomfield, NJ 07003.

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## CONTINUING EDUCATION CONFERENCE CALENDAR

### **April 1–8, 2006**

58th Annual Meeting of the American Academy of Neurology. Location: San Diego, Calif. Contact: American Academy of Neurology Member Services, 1080 Montreal Avenue, St. Paul, MN 55116; (800) 879-1960; fax: (651) 695-2791; e-mail: membership@aan.com; Web site: www.aan.com.

### **April 22–25, 2006**

38th Annual Meeting of the American Association of Neuroscience Nurses. Location: San Diego, Calif. Contact: AANN, 4700 W. Lake Avenue, Glenview IL 60025; (888) 557-2266 (US only); (847) 375-4733; fax: (877) 734-8677; e-mail: info@aann.org; Web site: www.aann.org.

### **May 31–June 3, 2006**

2006 Annual Meeting of the Consortium of Multiple Sclerosis Centers. Location: Scottsdale, Ariz. Contact: Tina Trott, Executive Assistant, CMSC, c/o Gimbel MS Center, 718 Teaneck

Road, Teaneck, NJ 07666; (201) 837-0727 ext 120; fax: (201) 837-9414; e-mail: tina.trott@mscare.org; Web site: www.mscare.org.

### **September 2–5, 2006**

10th Congress of the European Federation of Neurological Societies. Location: Glasgow, UK. Contact: EFNS Head Office, Breite Gasse 4–8, A-1070 Vienna, Austria; +43 1 889 05 03; fax: +43 1 889 05 03 13; e-mail: headoffice@efns.org; Web site: www.kenes.com/efns2006.

### **September 27–30, 2006**

22nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Location: Madrid. Contact: AKM AG, Clarastrasse 57, PO Box CH-4005, Basel, Switzerland; +41 61 686 77 77; fax: +41 61 686 77 88; e-mail: info@akm.ch; Web site: www.akm.ch/ectrims2006.



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