What Is the Promise of Stem Cell Research in MS?

Stem cell research is probably one of the most media-hyped—as well as one of the most promising—areas of medical research today. Mainstream news reports often focus on the political and ethical controversies surrounding the issue. Others present a list of diseases that stem cell treatments may eventually cure, including multiple sclerosis (MS). How realistic are such expectations? Anyone who is not a neurobiologist may have difficulty separating the facts from the myths—or the science from the sensationalism—in such a complex field of research. A better understanding of the issue begins with some basic definitions, according to Evan Snyder, MD, PhD, Director of the Stem Cells and Regeneration Program at the Burnham Institute in La Jolla, California.

There are three types of stem cells (Table). Pluripotent embryonic stem cells are undifferentiated cells that have the potential to produce any kind of cell in the body, explained Dr. Snyder. They have not yet learned their “address”—for instance, whether they are destined for the nervous system, blood, or muscle.

Multipotent somatic stem cells, (often incorrectly referred to as “adult” stem cells) are still plastic, but have learned what their destination is meant to be. These somatic cells are usually defined by two criteria: they are able to reproduce themselves throughout a life span, and they can give rise, in stages, to “differentiated,” or specialized, fully functional tissue cells under appropriate stimuli. “Somatic stem cells put an organ together and then maintain its balance and health all throughout life. It is the kind of stem cell that all other stem cells try to emulate,” said Dr. Snyder.

In addition, stem cells are categorized according to their source, as either somatic/multipotent or embryonic/pluripotent. Embryonic stem cells are derived from four- to five-day old blastocysts (a stage of development after fertilization), which have about 150 cells: 120 that are destined for the placenta and membranes, and 30 that form the embryo.

Somatic stem cells are generally able to differentiate only into cell types found in their tissue of origin. Another difference is that it is relatively easy to grow large numbers of embryonic stem cells in culture, while somatic stem cells are rarer in mature tissues and are difficult to extract. In addition, methods for increasing the number of somatic stem cells in culture have not been adequately developed. This is an important distinction because large numbers of cells are needed for stem cell replacement therapies.

In 1998, Dr. Snyder and colleagues were the first to isolate true
nervous system stem cells from the brains of humans and to demonstrate that they could integrate into the mammalian brain, respond to normal developmental cues, replace missing nerve cells, and perform gene therapy. These were the first human multipotent solid organ somatic stem cells isolated. During the same year, a group led by developmental biologist James Thomson, PhD, was able to isolate human pluripotent embryonic stem cells. “Which type of stem cell will be most useful for which diseases remains an area of active investigation,” said Dr. Snyder. “However, taken together, the recognition of the power of the embryonic stem cell created a revolution in scientific thought and research because of its potential to become missing cells in the body.”

**REGENERATIVE MEDICINE**

Cell replacement strategies are of particular interest for CNS diseases such as MS because, unlike many other tissues, the mature brain and spinal cord have a limited ability for self-repair. Current MS disease-modifying therapies deal mainly with the inflammatory and immunologic aspects of the disease, said Dr. Snyder. They attempt to prevent future damage, rather than repair damage that has already occurred. Current research suggests that the efficacy of these treatments is mainly restricted to the inflammatory phase of the disease, rather than to later stages, when neurologic damage increases.1

“We are starting to learn that cell replacement, while possible, is not enough,” Dr. Snyder admitted. “We’ve got to confer resistance to the cells.” In other words, if the host, or environment, that damaged the original cells is still present, similar processes may injure the replaced cells. “In MS, for example, we want to take the stem cell and lead it down a pathway that will create oligodendrocytes,” he said, “and that certainly can happen.” However, scientists are also starting to learn that the neuron itself might be damaged and might need to be replaced as well. “We want the oligodendrocyte to myelinate the damaged neuron. We also want the astrocyte to provide detoxification, growth by injury or disease. Stem cells offer a possible source for replacement strategies for cells damaged by MS, including oligodendrocytes, astrocytes, axons, and neurons.

**WHY CELL REPLACEMENT IS NOT ENOUGH**

"Stem cell therapies represent a regenerative approach that may offer a much-needed dimension to current MS therapies," Dr. Snyder explained. In regenerative medicine, the goal is to replace, repair, and regenerate cells, tissues, and organs in order to restore biological function that has been halted or compromised...
factors, and support,” he added. “We are finding out a very nice thing about the stem cell—it has the potential to provide a whole neighborhood of cells. We are also beginning to learn that the stem cell—even when it is not a neuron or an oligodendrocyte—can perform anti-inflammatory functions in and of itself.”

**STEM CELLS AND THE “SHIVERER MOUSE”**

A 1999 article by Dr. Snyder and colleagues\(^2\) provided the first evidence from animal studies that neural stem cells could be used to repair damage from brain disorders such as MS, where oligodendrocytes are needed and where cell dysfunction is global, or spread throughout the brain. Neurobiologists previously believed that the promise of these cells was limited to disorders such as Parkinson’s disease (PD), in which damage is restricted to specific areas of the brain.

In this study, neural stem cells were injected into the brain ventricles of newborn mice from an animal model called the “shiverer mouse” that develops severe tremors by two to three weeks of age. The tremor develops because the mice lack a key protein needed to make myelin. The condition mimics the defect seen in many human demyelinating disorders, including MS. Most of the transplanted cells migrated throughout the brain and matured into normal-looking oligodendrocytes, said Dr. Snyder. “These oligodendrocytes produced a significant amount of the missing myelin basic protein and began to myelinate nearby nerve fibers just as normal oligodendrocytes would. Moreover, tremors disappeared almost completely in 60% of the mice that received the transplants.”

Interestingly, neuronal stem cells transplanted into the brains of the shiverer mice were more likely to form oligodendrocytes than those transplanted into the brains of normal mice. “The stem cells differentiated into oligodendrocytes, which wrapped around the host axons and produced fairly thick, respectable myelin compared with the untreated mice,” said Dr. Snyder. This suggests that the neural stem cells somehow sensed that an oligodendrocyte-produced factor was missing in the mutant mice and attempted to compensate for the problem, he noted. “This provided evidence that stem cells can distribute enzyme factors and cells throughout the brain in a way that homes in on pathology, which is going to be an important paradigm for how we may approach a whole host of diseases, including MS,” he added. “The idea is to take the stem cell, put it into the brain, get it integrated—almost in a Trojan horse fashion—and have it create the cells needed in a particular environment.” In later studies, Dr. Snyder and colleagues were able to show that even stem cells injected into the bloodstream could find pathology in the brain and express proteins.

In a study published in *Nature* in 2003, Pluchino et al\(^3\) looked at stem cell behavior in autoimmune encephalomyelitis (EAE), an animal model of MS. Using Dr. Snyder’s technique, the researchers injected neural stem cells into the blood vessels of the animals. These stem cells found their way to the demyelinated areas of the brain and spinal cord. “This study showed that neural stem cells administered by blood vessel could start to make myelin in some of these EAE animals,” noted Dr. Snyder. “Some of the animals had a diminution of symptoms from EAE, including better nerve conductions.”

**WHAT IS THE NEXT STEP?**

“Are we simply going to be the best mouse doctors around, or is there any hope of translating this to human stem cell therapies?” Dr. Snyder asked half-jokingly. “So far, we have been able to put human cells in a primate and the cells became neurons, oligodendrocytes, and astrocytes. Also, in monkey models of human disease such as PD, we think we are seeing some benefits. Theoretically, this process should work the same way in humans.”

There are still numerous barriers to developing effective stem cell treatments in humans. Immune rejection (which is perhaps one of the biggest potential obstacles faced by stem cell researchers), unknown or unforeseen side effects, and limited availability of safe and effective stem cell lines are among the issues yet to be resolved. Although the use of somatic stem cells would solve the problem of immune rejection (if obtained from the actual recipient patient), it has not been demonstrated that somatic stem cells—especially if obtained from an adult—offer the kind of plasticity offered by embryonic or fetal somatic stem cells.

**REFERENCES**

CMSC MISSION STATEMENT
“To enhance collaboration of members for the improvement of care and the acquisition of knowledge. To increase resources and to transmit information, for the benefit of those affected by multiple sclerosis.” The CMSC will accomplish this mission through programs of comprehensive care, education, and research.

Core Purpose: To maximize the ability of multiple sclerosis (MS) health care providers to impact the care of people who are affected by MS, thus improving their quality of life.

CMSC ADVOCACY STATEMENT (NOVEMBER 12, 2004)
The CMSC understands that MS health care providers are receiving numerous calls from patients regarding Cochrane Review reports that question the efficacy of all therapies approved for relapsing-remitting MS (RRMS). This statement was intended to put these reports into perspective with the overwhelming evidence that led to the worldwide approval of the four available therapies for RRMS.

Leading neurologists, researchers, and thought leaders in the MS community, including the American Academy of Neurology, the National Multiple Sclerosis Society, the Canadian MS Clinics Network, and the Multiple Sclerosis Society of Canada, endorse the efficacy of Copaxone® (glatiramer acetate) and the three approved interferon products, Avonex®, Betaseron®, and Rebif®.

In addition to the pivotal trial data on these products, there are now additional longer-term data on the interferons and glatiramer acetate that support the long-term benefits of these products. The growing clinical use of the agent glatiramer acetate by experienced MS physicians around the world supports the continued need for the availability of this agent.

Kenneth Johnson, MD, Director of the Maryland Center for MS, Past President of the CMSC, and lead investigator in the trials of interferon beta-1b and glatiramer acetate, states, “The clinical trials leading to approval of these drugs were conducted with impressive scientific rigor. The use of these agents by MS patients and their physicians for more than a decade is convincing proof of the long-term treatment value of these drugs.”

The CMSC, the largest professional organization dedicated to MS care, strongly supports the recommendations of US and Canadian MS societies and advocates the use of the four approved therapies. We encourage patients to work with their neurologists to select and remain on the appropriate therapy to best manage their disease.

MULTIPLE SCLEROSIS CERTIFIED SPECIALISTS
On August 14 through August 28, 2004, candidates took part in the first certification examination for Multiple Sclerosis Specialists developed by the Clinical Care Committee and the Professional Testing Corporation. The successful candidates are now eligible to use the registered designation of Multiple Sclerosis Certified Specialist (MSCS). The second sitting of the exam will take place from February 12 through February 26, 2005. Those interested can obtain further information by contacting the Professional Testing Corporation at www.ptcny.com.

LIST OF PASSING CANDIDATES

| Elizabeth S. Auld | Susan K. Falck | Michelle E. Moats | Robert Tillett, Jr. |
| Chowdry Mujahid Bashir | Marcia Finlayson | Erin B. Moriarty | Toni L. Vandenberg |
| Patricia Bednarik | Jack H. Florin | Karen M. Nichols | Desiree L. Voita |
| Holli L. Benge | Cynthia A. Gackle | Karrie A. Page (C) | Monica A. Wainio |
| Susan E. Bennett | Smaranda A. Galis | Tracey L. Reeves | Jay M. Waller |
| Patricia Bobryk | Sharon L. Garcia | Kelly A. Ridge | Roger S. Williams |
| Lucille A. Boyle | Emily J. Griffin | Pamela J. Rieser | Sandra Williamson |
| David W. Brandes | Jacqueline A. Hall | Emily S. Riser | Roberta A. Winter |
| Terri A. Brewen | Ty D. Heuer | Gregory Sanandres | Greg R. Zarelli |
| Timothy Carrabine | Cynthia J. Hiiva | Karen L. Schultz (C) | |
| Tara L. Chay | Samuel F. Hunter | Deborah Sobotka | |
| Ellen M. Cloyd | Jennifer A. Kugies | Tara M. Stablein | |
| Lawrence Corbett | Ramona B. Maciejny | Maria B. Taylor | |
| Lily I. Duong | Michele Messmer (I) | Merle L. Teetzen | |

All USA except: I = Italy; C = Canada
IOMSN Announces New Mentorship Program

The IOMSN recently implemented a Nurse Mentorship Program. MS nurses who participate in this new program will have the opportunity to acquire the skills and knowledge needed to provide the highest quality of specialized MS nursing care and to become active participants in the MS clinical community, explained Colleen Harris, RN, NP, Chair of the Education Committee of the IOMSN.

The Nurse Mentorship Program is intended for nurses who are new to the field or who are planning to become involved in MS care. “This program will give nurses the opportunity to practice under the tutelage of an MS nursing expert,” noted Ms. Harris. “It will also provide participants with a core curriculum of key peer-reviewed articles and references so they can update their theoretical knowledge of MS.” After completing the program, apprentice nurses will be eligible for funding to cover the registration fee for the MS Certified Nursing Exam.

Candidates must submit a detailed application form, along with a letter of recommendation, to the IOMSN. The application will then be reviewed by the Mentorship Committee.

“We will provide each candidate with a needs-assessment questionnaire outlining the various areas of MS nursing,” said Ms. Harris. “Each participant can then decide in which area he or she would like to focus during the mentorship experience.”

Once a nurse has been accepted into the program, the Mentorship Committee will match him or her with an appropriate mentor from the MS nursing community. The mentorship will last for two days and will ideally be completed in a continuous period, explained Ms. Harris. At program completion, both the mentor and the apprentice will complete a formal evaluation of the experience. “While currently limited to the United States, it is anticipated that this program may become an international model,” said Ms. Harris.

The IOMSN hopes to provide mentorship opportunities to approximately 50 nurses in the program’s first year. Qualified nurses who are interested in becoming mentors for the program should contact the IOMSN by e-mail at info@iomsn.org. Candidates wishing to be matched with a mentor may obtain further information from the IOMSN Web site at www.iomsn.org. The application process is ongoing and candidates will be notified as soon as a decision is reached.

MS nurses who participate in the new Nurse Mentorship Program will have the opportunity to acquire the skills and knowledge needed to provide the highest quality of specialized MS nursing care.
Employment Issues in MS
Keeping MS Patients Working

Unemployment is an unfortunate, though common, reality following a diagnosis of MS. Although they are employed full time at the time of diagnosis, the majority of adults with MS become unemployed at some point after being told that they have the disease. One study showed that loss of income due to unemployment may account for up to 75% of the total cost of MS.

Workplace accommodations for individuals with disabilities have made it possible for many people with MS to continue working. However, many MS patients are not receiving appropriate vocational rehabilitation, according to Diane Playford, MD, FRCP, Senior Lecturer/Honorary Consultant Neurologist at the Institute of Neurology and the National Hospital for Neurology and Neurosurgery in London. During her talk on work retention in MS at the recent MS Trust meeting in Harrogate, United Kingdom, Dr. Playford stressed the importance of developing services that encourage MS patients to remain employed for as long as possible.

“Studies show that the high unemployment rates for individuals with MS are similar throughout the world,” said Dr. Playford, citing data from the United States, Canada, and Europe. “However, the same studies show that the level of disability of most of these patients is relatively low,” she added. “Many people with MS are leaving work when they’re still relatively mobile.” For example, in one study 77% of participants with MS were unemployed, even though most could walk independently.

Improving Vocational Services for People With MS

Dr. Playford and colleagues surveyed MS patients to determine what employment advice they had received in the past and what kinds of vocational services they would be interested in receiving. “We asked 100 patients of all ages and with varying subtypes of MS,” Dr. Playford reported. “Of those we surveyed, only 20% had actually received any type of employment advice.” Most of the vocational advice had been obtained from a hospital occupational therapist (OT). “It was interesting to note,” said Dr. Playford, “that well over half of those surveyed said they wanted this advice but didn’t know where to obtain it. Yet, when we developed such a service, we were unable to recruit enough patients.”

Based on the results of the survey, Dr. Playford and her colleagues came up with several suggestions to help improve vocational rehabilitation services for people with MS. “A vocational service should fit the needs of patients and provide them with the information and therapy they require,” she said. Programs should involve a multidisciplinary team, not just OTs. For example, MS nurses and other health care professionals can help to develop strategies for managing symptoms such as fatigue and incontinence, which may interfere with work. In addition, psychologists could help patients with cognitive problems involving memory and/or concentration. “These programs need to be well-funded in order to employ an appropriate staff,” she added.

Perhaps most importantly, people with MS need to be made aware that such a service exists. “As clinicians, we need to start querying our patients about their employment history and instructing them about where to go to receive help.

“It sounds obvious,” said Dr. Playford, “but a vocational program should be one that people actually want to attend. For instance, the language we use in vocational rehabilitation may be perceived as disparaging. We should avoid using terms like ‘work evaluation.’ Patients may hear those words and feel that their performance will be scrutinized and judged.”

Convenience and accessibility are also important issues, Dr. Playford stressed. “If someone is disabled, has a job, and/or has responsibilities at home, it may be difficult for that person to spend a day or a week at a hospital to attend a vocational rehabilitation program. We need to be flexible in the way we structure our programs.”

She pointed out that current vocational rehabilitation tends to focus on getting individuals who are disabled back to work. “However, this is not usually the main issue in the MS population; most patients are already employed at the time they are diagnosed,” she noted.

Shifting Attitudes

“Health care providers should be encouraged to join with occupational and vocational therapists to try to keep MS patients working for as long as possible,” she stressed. “In order to accomplish this, we first need to create a shift in health care workers’ attitudes.” For ex-
ample, she noted that many clinicians simply do not inquire about the work-related needs of their MS patients. “We audited the OT outpatients at our clinic and found that, while 18 of 20 had work-related needs, only two had been referred for those reasons.” The clinicians had either downplayed the significance of the issue or hadn’t realized it was a problem that should be addressed. “MS health care providers need to realize how important remaining at work is in many of their patients’ lives and encourage rather than discourage the continuation of employment,” she said.

“The rewards of continuing to work for people with MS can be much more than financial; employment can create a sense of purpose, personal fulfillment, and a feeling that one is contributing to society, which is especially important in light of the depression and despair that are so common in people with MS,” Dr. Playford pointed out. “Anyone who wishes to remain at work should have every opportunity to do so. Hopefully, we can make that a reality.”

MSX—Krista Binetti

“Health care providers should be encouraged to join with occupational and vocational therapists to try to keep MS patients working for as long as possible,” Dr. Playford stressed.

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Understanding and Managing Bowel Dysfunction in MS

Bowel dysfunction is especially common in diseases like MS that affect the nerves and muscles. In fact, up to 70% of individuals with MS report constipation and/or fecal incontinence.1 Bowel complications can negatively affect everyday life, contributing to embarrassment, feelings of anxiety, and, often, an inability to work or to engage in social activities. At the recent MS Trust conference in Harrogate, UK, Christine Norton, PhD, RN, discussed bowel dysfunction in MS and offered some insight on treating and managing this condition.

Professor Norton, a nurse consultant at St. Mark’s Hospital and Professor of Nursing at King’s College, both in London, pointed out that despite its high prevalence in the MS population, little is known about the impact of bowel dysfunction on those with the disease. “Of 18,000 articles on MS published in medical journals over the last 30 years, only 30 have focused on bowel dysfunction and not one was a treatment study,” Prof. Norton noted.

Symptoms related to the bladder and the bowel are rated by patients as the third most common factor limiting their ability to work (after spasticity and incoordination).1 “Those with bowel problems obviously experience a reduced quality of life as well,” Prof. Norton said. “They may avoid places and activities where a rest room is not readily available.”

How MS Affects the Bowel

Prof. Norton discussed how the physical changes that occur in MS also may affect the bowel. “MS impacts the sensory and motor function of the anorectum,” she explained. “This contributes to reduced sensation. In effect, the call to have a bowel movement becomes blunted, leading to constipation. A host of other MS-related causes, such as slow colonic transit and failure of the puborectalis muscle to relax may also contribute to the condition.

“Conversely, the striated muscles of the external anal sphincter and pelvic floor may become weak or uncoordinated, so individuals may not be able to resist the urge to have a bowel movement.” All of this probably results from a combination of central nervous system lesions and autonomic dysfunction, she explained.

“While bowel disorders are associated with more severe disability and greater disease progression, they
are not associated with gender nor necessarily with bladder problems,” Prof. Norton added. These complications also do not appear to show specific patterns among the different subtypes of MS.

**Determining the Cause**

Prof. Norton cautioned clinicians against assuming that an individual is experiencing bowel dysfunction based on the presence of MS. “Childbirth or other anal sphincter trauma, rectal prolapse, and irritable bowel syndrome all may contribute to fecal incontinence, while constipation may be attributed to a host of other causes as well as to MS.”

To confirm that bowel-related symptoms are related to MS, “a comprehensive history of the patient should be taken and a complete physical examination should be performed,” Prof. Norton said. A colonoscopy also may be warranted, especially in the presence of a change in bowel habits or rectal bleeding.

**Treating the Problem**

Some nonpharmacologic methods may initially be helpful to patients with constipation, she suggested. “It is important to educate the patient about normal bowel activity,” she said. In addition, patients should be made aware of the importance of consuming adequate amounts of fiber and fluids. Those taking medications should be advised to review them with their clinician and to ask if it’s possible to change any medicine that may be causing constipation. As a last resort, she adds, low-dose laxatives or glycerin suppositories may be prescribed.

“As troubling as constipation may be,” Prof. Norton noted, “fecal incontinence can be much more distressing for individuals with MS, causing anxiety and limiting their ability to work and interact socially.” Prof. Norton said that treatment is mostly a trial-and-error process. “Pelvic floor exercises and vaginal electrical stimulation have been shown to help manage urinary incontinence but, as of yet, there is no evidence to recommend these treatments for fecal incontinence. Some options may include drugs such as loperamide (Imodium®) and, in severe cases, surgical interventions, she said. In 2000, a study published in the *Journal of Neurology, Neurosurgery, and Psychiatry* suggested that biofeedback may be effective for certain individuals with MS who also experience constipation and fecal incontinence. Of 13 MS patients who underwent the treatment, five showed a positive response. “However, a response was more likely for those patients who experienced limited disability and whose disease course was not progressive,” Prof. Norton added.

“There is an urgent need for greater public awareness of bowel dysfunction in individuals with MS,” Prof. Norton stressed. “People delay seeking treatment for these problems, perhaps due to a perceived lack of clinical services. Patients should be questioned by clinicians with regard to their bowel function, as they may be hesitant to bring up the issue themselves. Finally, we as clinicians should conduct further research into effective treatment options for this common and often debilitating condition.”

—Krista Binetti

**REFERENCES**


Quality of life (QoL) issues are of utmost importance when treating patients with a lifelong, progressive, and incurable disease such as multiple sclerosis (MS). Disease-modifying treatments, patient education, peer support groups, and other forms of social support may be sufficient to address many QoL issues affecting people in mild to moderate stages of MS. However, many people with more severe disease may require an approach that is more focused on comfort and provides more frequent and direct care from health care professionals. According to a presentation by Candy Cooley, MMed Sci, RGN, RSCN, at the recent MS Trust conference in Harrogate, United Kingdom, a palliative care approach may best benefit such patients.

During her talk, Ms. Cooley, who is Palliative Care Development Manager in Worcestershire, UK, cited the World Health Organization (WHO) definition of palliative care as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness through the prevention and relief of suffering by means of early identification of pain and [physical, psychological, and spiritual] problems.” WHO also lists several of the goals of palliative care, many of which are appropriate for the care of people severely affected by MS, said Ms. Cooley (Table 1).

The modern philosophy of palliative care began with the hospice movement, which gained momentum in the UK after the founding of the first modern hospice in 1967 by Dr. Cicely Saunders. Hospice care promoted the idea of specialized care for the dying. The practice of palliative care, whether in hospice, hospital, clinic, or the patient’s home, is mainly geared toward terminally ill cancer patients. As reflected in the WHO definition, however, the philosophy and practice of palliative care is starting to extend its scope to include people with other (mostly) incurable, progressive, and debilitating diseases, including MS.

Palliative Care in MS: Issues and Obstacles

“There needs to be a considered approach regarding health-related QoL for people with severe MS,” said Ms. Cooley. A meta-analysis of surveys that measured QoL outcomes in MS patients by Gruenewald et al. identified several issues of importance to people with severe MS (Table 2). However, much more research in this area is necessary so the needs of patients in advanced stages of MS can be better addressed, Ms. Cooley stressed.

Palliative care is ideally provided by a core interdisciplinary team consisting of physicians, nurses, chaplains, social workers, and other health care professionals. In fact, one of the key characteristics of palliative care is that it involves this multidisciplinary approach, Ms. Cooley emphasized. The difficulty lies in establishing this network of professionals beyond the hospice setting and practically applying this teamwork approach to people with MS in clinical, community, and home care settings, an idea which has emerged only recently. “Close working relationships between palliative care and MS specialists, who can consider the needs of patients and families from different perspectives, will enhance the delivery of appropriate care,” she noted.

In addition, there is the problem of the “specialist versus generalist debate,” Ms. Cooley pointed out. Although there are palliative care specialists in both the UK and the United States, several questions need to be considered:

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<td><strong>Main Goals of Palliative Care</strong></td>
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<tr>
<td>• Provides relief from pain and other distressing symptoms</td>
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<td>• Affirms life and regards dying as a normal process</td>
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<td>• Intends neither to hasten nor to postpone death</td>
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<td>• Integrates the psychological and spiritual aspects of patient care</td>
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<td>• Offers a support system to help patients live as actively as possible until death</td>
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<tr>
<td>• Offers a support system to help the family cope during the patient’s illness and in their own bereavement</td>
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<tr>
<td>• Uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated</td>
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<tr>
<td>• Will enhance quality of life and may also positively influence the course of illness</td>
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Source: World Health Organization. WHO definition of palliative care.2

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<th>Table 2</th>
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<td><strong>Quality of Life Issues Important to People With Severe MS</strong></td>
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<tr>
<td>• Mental health problems such as depressed or anxious mood</td>
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<td>• Loss of dignity related to dependency in daily activities</td>
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<td>• Difficulties in accepting losses and lack of control in the face of a progressive and unpredictable disease course</td>
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<tr>
<td>• Support from others</td>
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<tr>
<td>• Impaired functioning in social and family settings</td>
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<tr>
<td>• Symptoms such as fatigue and visual impairment</td>
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Source: Gruenewald et al. Mult Scler. 2004.1
How “specialized” do these health care providers need to be? What types of educational requirements are necessary? Are palliative care specialists, who are mostly trained to meet the needs of cancer patients, qualified to meet the needs of people with MS? What kind of additional training is necessary? “Unfortunately, there currently is little training available that addresses palliative care needs of those with nonterminal conditions such as MS, which is one of the biggest obstacles we face,” said Ms. Cooley.

—Rosalee L. Blumer

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On November 23, 2004, the FDA approved natalizumab (Tysabri®) for the treatment of relapsing forms of MS. The accelerated approval was granted based on the positive one-year data from two placebo-controlled trials involving approximately 2,100 patients with relapsing MS. As a condition of approval, trials will continue for another year.

Natalizumab is a monoclonal antibody that works by blocking certain types of white blood cells (T lymphocytes) from entering the CNS. “Natalizumab is an adhesion molecule inhibitor that is designed to bind to alpha4-integrin,” explained Julie Saunders, Product Manager, Nursing Programs and Initiatives for Biogen Idec, the drug’s manufacturer. “It inhibits the migration of immune cells into tissues where they may cause or maintain inflammation.”

In a phase III MS trial called AFFIRM involving 942 patients with relapsing-remitting MS, natalizumab was superior to placebo in the primary end point of annualized relapse-rate reduction (66%) and the secondary end point of reduction in brain lesion activity at one year, according to Ms. Saunders.

After one year, 60% of natalizumab-treated patients were free of new or newly enlarging T2 lesions (vs 22% on placebo); 96% were free of gadolinium-enhanced lesions (vs 68% on placebo); and 76% were relapse free (vs 53% on placebo).

FDA APPROVES MONOCLONAL ANTIBODY TREATMENT FOR MS

RESEARCHERS FIND LINK BETWEEN BIRTH MONTH AND RISK OF MS

The risk of developing MS is greatest for people born in May and lowest for those born in November, at least for those in the northern hemisphere, say researchers from the Canadian Collaborative Study Group. According to their recent study published in BMJ, factors related to the month of a person’s birth may interact with his or her genetic risk of acquiring the disease.

The investigators looked at data from more than 42,000 MS patients from northern countries where the prevalence of MS is high. In a combined sample of Danish, British, Swedish, and Canadian data, significantly more people with MS were born in May (9.1%) and significantly fewer were born in November (8.5%). This represents a 19% decreased risk of MS for people born in November compared with those born in May. MS patients with a family history of the disease showed a similar pattern, with an even stronger association between birth month and MS. The highest ratio of May/November risk was observed in Scotland, where the population prevalence of MS is highest.

Although the researchers believe the association of birth month and MS risk was proven conclusively in this study, they admit the reason for the link is unclear. Low maternal folate levels and low infant birth weight are possible risk factors; however, many other factors have yet to be identified. Previous studies suggest that a seasonal deficiency in vitamin D in pregnant women in northern-latitude countries may play a part in the development of MS in their children. Studies of half-siblings with MS have shown a maternal “parent of origin” effect in developing the disease.

The authors conclude that “the risk factor(s) responsible for the effect of timing of birth must vary seasonally and probably interacts with development of the central nervous system or immune system, or both.”


LITERATURE MONITOR/NEWS ROUNDPUP

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A one-year analysis of a pivotal phase III MS trial called SENTINEL, which enrolled 1,171 patients with relapsing forms of MS, evaluated the addition of natalizumab to interferon beta-1a (Avonex®). Compared with interferon beta-1a alone, combination therapy with natalizumab produced a 54% additional reduction in relapse rate. Furthermore, of those treated with the combination, 67% were free of new or newly enlarging T2 lesions (vs 40% of those on interferon beta-1a plus placebo) and 96% were free of gadolinium-enhanced lesions (vs 76% of those on interferon beta-1a plus placebo).

Natalizumab is infused over approximately one hour at a recommended dose of 300 mg IV every four weeks. “It is recommended that patients remain under supervision for one hour post-infusion,” Ms. Saunders said.

Natalizumab was generally well tolerated in the clinical trials. “More than 1,600 patients were included in the safety database, with a median time of exposure to the drug of 20 months,” noted Ms. Saunders. An important safety consideration is the risk of serious hypersensitivity reactions (eg, urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain), which occurred in approximately 1% of patients in clinical trials. The most frequently reported serious adverse reactions were infections (2.1% vs 1.3% placebo), hypersensitivity reactions (1.3%, including anaphylaxis/anaphylactoid reaction 0.8%), depression (0.8%), and cholelithiasis (0.8%).

Combination Therapy May Benefit Suboptimal Responders

The combination of immunomodulators and immunosuppressant drugs may be more beneficial than either drug class used alone for the treatment of MS, according to a recent article in Neurology by Douglas R. Jeffery, MD, PhD.

Dr. Jeffery reported that the combination of mitoxantrone and interferon beta may reduce relapse rate, decrease the frequency of enhancing lesions on MRI, and decrease the T2 lesion burden. In addition, this combination appears medically safe, according to preliminary studies.

Dr. Jeffery noted that even high doses of interferon beta are often insufficient to completely suppress inflammatory disease activity in patients with relapsing-remitting MS or secondary progressive MS. He cited a study published in 1997 in Neurology by Stone et al that followed MS patients with monthly MRI scans. Only 40% showed complete suppression of new enhancing lesions after starting interferon beta-1b therapy, which “represents a clearly suboptimal response,” said Dr. Jeffery.

Several studies conducted in the past decade have shown the efficacy of mitoxantrone when combined with other MS disease-modifying agents in decreasing relapse rates, progression of disability, and MRI measures of disease activity. One pilot study showed that mitoxantrone combined with interferon beta-1b produced a 70% decrease in relapse rate when compared with the baseline phase of the study in which patients were taking interferon beta-1b only. The addition of mitoxantrone did not decrease the efficacy of the interferon.

Before using combination therapy in MS patients, clinicians should review available data to ensure that the use of one agent will not block the effects of the other. They should also make sure that the combination is medically safe in terms of risks for toxicity, cautioned Dr. Jeffery. Because cardiotoxicity is a possible serious adverse effect of mitoxantrone treatment continuing longer than 2.5 years, he stressed that combination therapy should not be used unless MS patients definitively show a poor response to standard treatment. However, he also advised that combination therapy “should not be delayed until disability is advanced.” He suggested that patients with continued progression of MS despite standard therapy receive early intervention with combination therapy “to prevent or delay the development of advanced disability.”

CONTINUING EDUCATION CONFERENCE CALENDAR

April 8–11, 2005
37th Annual Meeting of the American Association of Neuroscience Nurses. Location: Washington, DC. Contact: AANN, 4700 W Lake Avenue, Glenview, IL 60025; (888) 557-2266 or (847) 375-4733; fax: (877) 734-8677; e-mail: info@aann.org; Web site: www.aann.org.

April 9–16, 2005
American Academy of Neurology 57th Annual Meeting. Location: Miami Beach, Fla. Contact: AAN Registration, 33 New Montgomery, Suite 1420, San Francisco, CA 94105; (651) 695-2717; fax: (415) 979-2260; e-mail: aann2005reg@cmrus.com; Web site: http://am.aan.com.

September 17–20, 2005
9th Congress of the European Federation of Neurological Societies. Location: Athens, Greece. Contact: EFNS Head Office, University Campus, Courtyard 1, Alser Strasse 4, A-1090 Vienna, Austria; +43 1 889 05 03; fax: +43 1 889 05 03 13; e-mail: headoffice@efns.org; Web site: www.efns.org.

CMSC 2005 ANNUAL MEETING

The 2005 Annual Meeting of the Consortium of Multiple Sclerosis Centers will take place June 1 to 5 in Orlando. The theme is “Navigating the World of Multiple Sclerosis.” Presentations will pertain to timely issues involving MS patient care and basic and clinical research, as well as those that reflect collaboration between specialties. Go to www.mscare.org for additional information, or contact Tina Trott, Executive Assistant, Consortium of Multiple Sclerosis Centers, c/o Gimbel MS Center, 718 Teaneck Rd, Teaneck, NJ 07666; (201) 837-0727 ext 120; fax: (201) 837-9414; e-mail: tina.trott@mscare.org.

September 25–28, 2005
130th Annual Meeting of the American Neurological Association. Location: San Diego, Calif. Contact: ANA, 5841 Cedar Lake Road, Suite 204, Minneapolis, Minn. (952) 545-6284; fax: (952) 545-6073; e-mail: ana@llmsi.com; Web site: www.aneuroa.org.

September 28–October 1, 2005
Joint Annual Meeting of ECTRIMS and ACTRIMS. Location: Thessaloniki, Greece. Contact: AKM Congress Service, PO Box CH-4005, Basel, Switzerland; +41 61 686 77 66; fax: +41 61 86 77 88; e-mail: info@akm.ch; Web site: www.akm.ch/ectrims2005.

November 13–15, 2005
MS Trust 9th Annual Conference. Location: Harrogate, UK. Contact: Packer Forbes Communications, 53 Cavendish Road, London, SW12 0BL; +44 20 8772 1551; fax: +44 20 8772 1552, e-mail: info@mstrust.org.uk; Web site: www.mstrust.org.uk.