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Publishers
Joseph J. D'Onofrio
Frank M. Marino
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Website: www.delmedgroup.com

Writer/Editor
Nancy Monson

Art Director
James Ticchio

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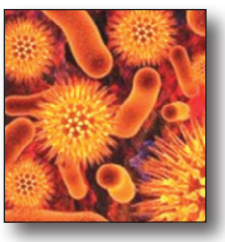

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A NEW WAY OF LOOKING AT PROGRESSIVE MS

When you have a progressive form of multiple sclerosis (MS), it's difficult to hear about all the advances that have been made in improving the lives of people with relapsing-remitting MS (RRMS), yet see how little forward motion has been achieved in understanding and treating progressive forms.

Until now. "There has been a big push by the National Multiple Sclerosis Society and the National Institutes of Health to shift funding from relapsing MS to progressive MS," reports Barbara J. Green, MD, medical director of The MS Center of Saint Louis and an *MS Perspectives* advisor. As a result, there is now a greater focus on trying to understand the causes of progressive MS, as well as to find better ways of recognizing when patients have transitioned from relapsing to progressive forms of the disease. New criteria have been introduced to define when the disease is active (new relapses, new lesions on magnetic resonance imaging [MRI] scans) and when it has become progressive (continuous worsening in clinical symptoms). "There are also a number of new treatment avenues in the pipeline," she says, such as ocrelizumab (Ocrevus™). This drug is given by intravenous

MS DEFINITIONS

RRMS: The most common type of MS in which a person has neurologic symptoms that come in the form of attacks (called relapses). In periods of remission, symptoms may go away completely—or they may remain long term in varying levels of severity.

SPMS: A form of MS that occurs in some people who have previously been diagnosed with RRMS. They continue to experience relapses, but they also have slow worsening of their disease between relapses. At some point, they may stop having relapses, but the transition to progressive disease is gradual and subtle, and it can be difficult to pinpoint when it is occurring.

PPMS: A form of MS where a person has a more gradual worsening of neurologic function from the time that symptoms first appear and doesn't have any relapses.

With all three forms of MS, healthcare providers now look to see whether the disease is active (causing relapses and/or changes on MRI scans) or not active and progressing (worsening with accumulating disability) or not progressing. "By putting the disease into these categories of active or not active, progressing or not progressing, it helps us to make decisions about treatment," explains Dr. Green.

(IV) infusion every 6 months and is currently under review by the Food and Drug Administration. The drug is categorized as a monoclonal antibody that targets immune cells (specifically, certain types of B lymphocyte cells) that are involved in MS. Ocrelizumab is the first drug to have demonstrated effectiveness in both RRMS and primary-progressive MS (PPMS) in trials that measured whether it decreased relapses, slowed the progression of disability, and prevented new MRI lesions. "In the PPMS trial, the rate of disability progression was significantly reduced," says Dr. Green.

How Progressive MS Differs from Relapsing MS

It is now understood that progressive MS differs from RRMS in some key ways. For instance, although demyelination (stripping of the protective coating around nerve cells) occurs

in both the white and gray matter of the brain in all forms of MS, it is thought that there may be more impact on the gray matter in progressive disease. (White matter is largely responsible for communication around the brain and body, while gray matter is where most of the brain's processing and cognition occur.) In addition, inflammation in the central nervous system (the CNS) appears to be more prominent in relapsing disease and less so in progressive disease. And the progressive forms of MS are believed to cause more degeneration (damage) in the CNS than inflammation. As a result, because most of the currently available drugs for MS produce their effects by reducing inflammation, they may not be as effective in progressive forms of MS as in relapsing disease.

Because there are fewer relapses to track in people with progressive MS and because changes on MRI scans become less

FYI

Did you know that...

- ***One million people worldwide have a progressive form of MS.***
- ***Fifteen percent of people with MS get an initial diagnosis of primary-progressive disease (PPMS).***
- ***Researchers are beginning to understand what causes progressive MS, how to monitor progression, and how to treat this form of the disease.***

prominent, it is often difficult for researchers and clinicians to measure and monitor how patients with progressive MS are responding to treatments. Now that may be changing. For instance, recent investigations using advanced imaging techniques show that people with progressive MS may have collections of immune cells in the meninges, the protective tissue that surrounds the brain and spinal cord. By following these types of changes in the body, healthcare providers may eventually have a way of better understanding their patients' conditions and helping them more.

Identifying patients with PPMS or those transitioning from RRMS to SPMS is going to be increasingly important as approved treatments for progressive forms of the disease become available on the market, says Dr. Green. Likewise, recognizing when ongoing treatment is no longer effective will also be crucial in an era of increasing options. "A person may have been stable on a particular treatment regimen for many years but start to have worsening symptoms or have changes on MRI scans, such as a loss of brain tissue, that suggest he or she is transitioning to SPMS," she explains. Today in these cases, healthcare providers have more options than ever before and can try a different approach to treatment. In fact, some clinicians are going "off-label" and using drugs that have been approved for other autoimmune diseases but are still being studied in MS, and they hope to use ocrelizumab if and when it becomes available.

"As more of these techniques and treatments are discovered and refined, they will move into clinical practice and they'll allow us to develop methods to intervene in the same way we have with relapsing MS," says Dr. Green. "There is hope."

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MS Disease-Modifying Drugs for Progressive and Relapsing MS

AN UPDATE

Drug development in relapsing-remitting multiple sclerosis (RRMS) has been quite exciting over the past few decades and continues apace. But according to *MS Perspectives*™ advisor Aliza Ben-Zacharia, DrNP, nurse practitioner at The Corinne Goldsmith Dickinson Center for Multiple Sclerosis at The Mount Sinai Medical Center in New York City, "research has also been on the rise to address the management of people with secondary-progressive MS (SPMS) and primary-progressive MS (PPMS)." Given that the immune system is the culprit in MS leading to inflammation, loss of myelin (the protective coating around nerve fibers), and neurodegeneration (destruction of the nerve fibers), multiple medications are being developed to modify or mildly suppress the highly active immune system. What's more, a couple of the medications are being given "Fast Track" status by the Food and Drug Administration (FDA) to speed the development and approval process along.

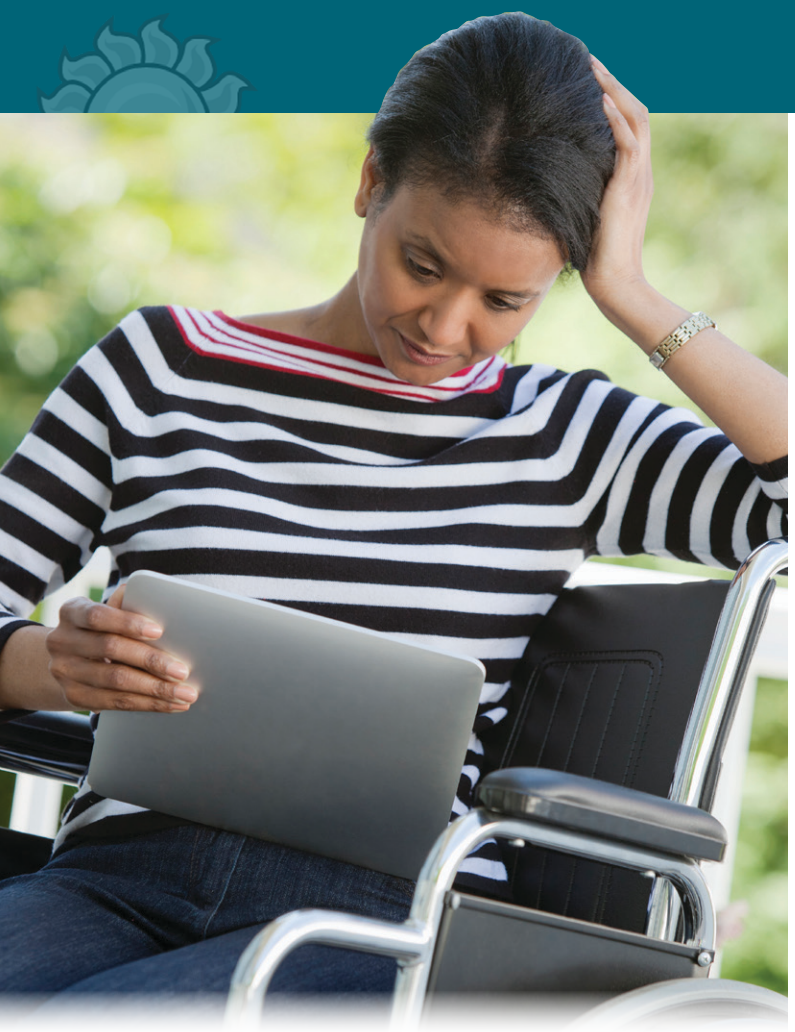
From Failure Comes Success?

The news on the progressive MS treatment front hasn't been very encouraging until recently. Disease-modifying therapies (DMTs) that work in relapsing MS, such as glatiramer acetate (Copaxone®), fingolimod (Gilenya®), and natalizumab (Tysabri®), haven't been shown to be effective in clinical trials, although clinicians sometimes prescribe them off-label for progressive MS—especially if people have

activity on their MRI scans. And researchers were very disappointed when a unique antibody called opicinumab failed to improve physical and cognitive function or to delay disability and disease progression in a recent study. In early testing, the drug blocked the actions of the LINGO-1 molecule, which is found in the central nervous system (CNS) and interferes with the body's repair of myelin and nerve fibers (axons). "This so-called anti-LINGO approach is a novel technology that has the potential to rebuild myelin and promote recovery, which would have been a major breakthrough in MS treatment," says Dr. Ben-Zacharia. "Still, there is some hope that the lack of effect in the recent trial might have been because too low a dose was used. A future study with a different dosing regimen for opicinumab might produce better results."

The Big News in PPMS

The big news in PPMS is ocrelizumab (Ocrevus™), a humanized monoclonal antibody. (Humanized means that the drug was created with human protein so that the body's immune system doesn't attack it.) The FDA has given ocrelizumab, which is administered intravenously every 6 months, "Fast Track" status for approval. Ocrelizumab has also shown effectiveness in relapsing forms of MS. Clinical trials called OPERA I and OPERA II tested ocrelizumab against the interferon drug Rebif®. These studies included 1,656 patients with RRMS or SPMS and showed a 46% to 47% reduction in relapses and a 94% to 95% reduction in new magnetic resonance imaging (MRI) lesions over 2 years. In a PPMS trial, called ORATORIO, ocrelizumab treatment significantly reduced the progression of disability among 732 patients with PPMS over 12 months. Serious adverse events were noted in the trial, including severe infusion-related reactions and several malignancies (which



may or may not have been caused by ocrelizumab). On the positive side, opportunistic infections—certain serious infections that can affect people with altered immune systems—that have occurred in trials of ocrelizumab in other autoimmune diseases such as rheumatoid arthritis did not occur in the MS studies.

A New Relapsing MS Drug

A new drug for relapsing MS has already been approved by the FDA this year and is now available in the US. Like ocrelizumab, daclizumab (Zinbryta™) is a humanized monoclonal antibody that affects the function of a signaling receptor that is known to be involved in causing MS. The DECIDE study of 1,841 patients with relapsing MS compared daclizumab to the interferon Avonex®. In this study, daclizumab produced a 45% reduction in the relapse rate and a 54% to 65% reduction in lesions seen on MRI scans. This medication is injected under the skin (subcutaneously) every 4 weeks. Safety issues include skin rash and hypersensitivity. In addition, the drug has the potential to cause some serious side effects, such as liver toxicity, colitis (inflammation of the lower bowel), enlargement of lymph nodes, and even death. For this reason, the manufacturer says daclizumab should "generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS."

Other MS Medications in the Pipeline

Several other promising DMTs are being studied:

Sphingosine 1-phosphate (S1P) receptor modulators. The oral MS drug fingolimod (Gilenya®) is one type of S1P receptor modulator that lowers the number of lymphocytes (immune cells) circulating in the blood—trapping

them in the lymph nodes where they are produced—which reduces their ability to attack the CNS. Other more selective S1P receptor agents are waiting in the wings: ponesimod, siponimod, ozanimod, ceralifimod, GSK2018682, and MT-1303. These drugs are still in the early stages of development, but results have been promising.

Laquinimod. This drug has anti-inflammatory properties and may even be protective of the CNS. Two studies—one in people with RRMS (a trial called CONCERTO) and another in those with PPMS (a trial called ARPEGGIO)—are currently ongoing with laquinimod.

Ofatumumab (Arzerra™). A monoclonal antibody, like ocreluzimab, ofatumumab was tested in a RRMS safety trial called MIRROR, the results of which showed it significantly reduced progression of the disease as seen on MRI scans. An upcoming phase III trial (the last phase of clinical trials needed for FDA drug approval) will monitor for side effects seen in the earlier study.

Ibudilast. This oral medication has anti-inflammatory and nerve-protection properties and is being tested in progressive MS, in early safety (phase II) trials that are due to be completed this year. Phase III trials will be needed to prove the drug is effective and safe in both relapsing and progressive forms of MS. Still, the drug has received "Fast Track" status from the FDA.

"The list goes on," says Dr. Ben-Zacharia, "and includes vaccines that treat the disease (rather than prevent it as we usually think of vaccines) and stem-cell therapies. That's why we are hoping to have real interventions soon for our patients with progressive MS, as well as even more treatment options for people with relapsing MS."

To learn more about MS research, visit the National MS Society's "MS Trials Alert" page at www.nationalmssociety.org/Research/Participate-in-Research-Studies/Participate-in-Clinical-Trials/MS-Trial-Alerts and the national government's page at www.clinicaltrials.gov.

Ask the Clinician

Q. I've heard that the bacteria in our stomachs may cause MS. Is that true?

A. Yes, they may be related. There is evolving research that suggests MS may be associated with the large diversity of bacteria and perhaps other microflora (viruses, fungi, and other micro-organisms), called the gut microbiome, that lives within all of us. We already know that there are many environmental risk factors for MS—vitamin-D deficiency, alcohol abuse, obesity, smoking, use of antibiotics, stress. The common source or denominator for all of these risk factors may be the gut microbiome. It also may be one that we can impact fairly easily.

The gut microbiome secretes a large range of products that are sensed by the brain, which in turn releases molecules controlling the motility (movement) and digestive processes of the gut. Current studies suggest that changes in the gut microflora and their products may alter the immune system, leading to demyelination (stripping of the protective padding around nerve fibers) in the central nervous system, the hallmark of MS. Alterations in gut microflora may also possibly lead to the remyelination that is essential for tissue repair and disease remission.

The microbiome is the combination of genetic material found in the bacteria, fungi, viruses, and other micro-organisms and their interaction with the host (in this case, the human body). All mucosal surfaces of living creatures, both plant and animal, have a microbiome. In humans and other mammals, the major microbiome is located in the gut. The bacteria alone may number up to 100 trillion cells—making it 10 times larger in size than the count of all of the cells in our bodies. Life would not be

possible without these "little friends," as they are part of our evolutionary development. For example, within each of us live certain types of bacteria known as Archae that date back 3 billion years. We need many of these bacteria, and they can have positive effects on our health.

The list of medical conditions that may be affected by the microbiome is expanding rapidly. We have found that there is probably an association between obesity, the gut microbiome, and immune responses seen in autoimmune disorders such as MS. We know that the composition of the gut microbiome changes as we age, with our diet, based on our genetic background and our body's functioning, and with the use of antibiotics. Because of these factors, the microbiome can be disrupted, and we can end up having too much of certain types of bacteria and too little of other types in our gut, which can tip the balance toward a bad health effect. For instance, if we eat a lot of red meats, eggs, trans fats, and salt, the microbiome may start producing inflammatory agents. In contrast, consumption of omega-3 fatty acids, such as found in fish oil and avocadoes, can trigger anti-inflammatory activity in the microbiome.

However, the gut is a very complex organ comprised of cells alien to our body (as each of us has over 1,000 different species of bacteria within us) and we are only at the very, very tip of the iceberg in understanding how these bacteria affect our bodies. Still, these research findings are exciting because they give us new avenues to explore for treatments. They also increase our understanding of what is driving MS, so that novel therapies that are far less disruptive to the patient's normal immune system can become available.

In short, the gut microbiome and its relation to human and animal disease may become the next great way of understanding human biology and medicine.

— *Lloyd H. Kasper, MD*
Department of Microbiology and Immunology
Geisel School of Medicine
Dartmouth College
Hanover, New Hampshire

What Is the Role of Stress in Multiple Sclerosis?

- Your threshold for tolerating stressful situations is lowered when you have a chronic illness like MS. Fatigue, cognitive issues, and the frustration of dealing with mobility limitations and other symptoms compound the everyday human experience of stress.
- Stressful life events can serve as a trigger for exacerbations/relapses in people with MS.
- Many people with MS suffer from depression, which is compounded by stress and has been shown to heighten inflammatory responses. This leads to a worsening of MS symptoms, which in turn leads to worsening depression.
- Stress in MS can become a kind of "vicious circle." It can worsen the perception of MS symptoms or the symptoms themselves, which can make it even harder to cope with the disease.
- Beneficial techniques for relieving stress differ for each individual. Some methods that have been proven to help people with MS manage stress while reducing fatigue and improving some other MS symptoms include yoga, meditation, and exercise.
- Using mindfulness "apps" for smartphones is one way to incorporate stress-reducing techniques into your daily schedule.
- Becoming aware of stress triggers and how stress-management techniques may offer relief can help you avoid a downward slide into a high-stress, illness-provoking state.

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