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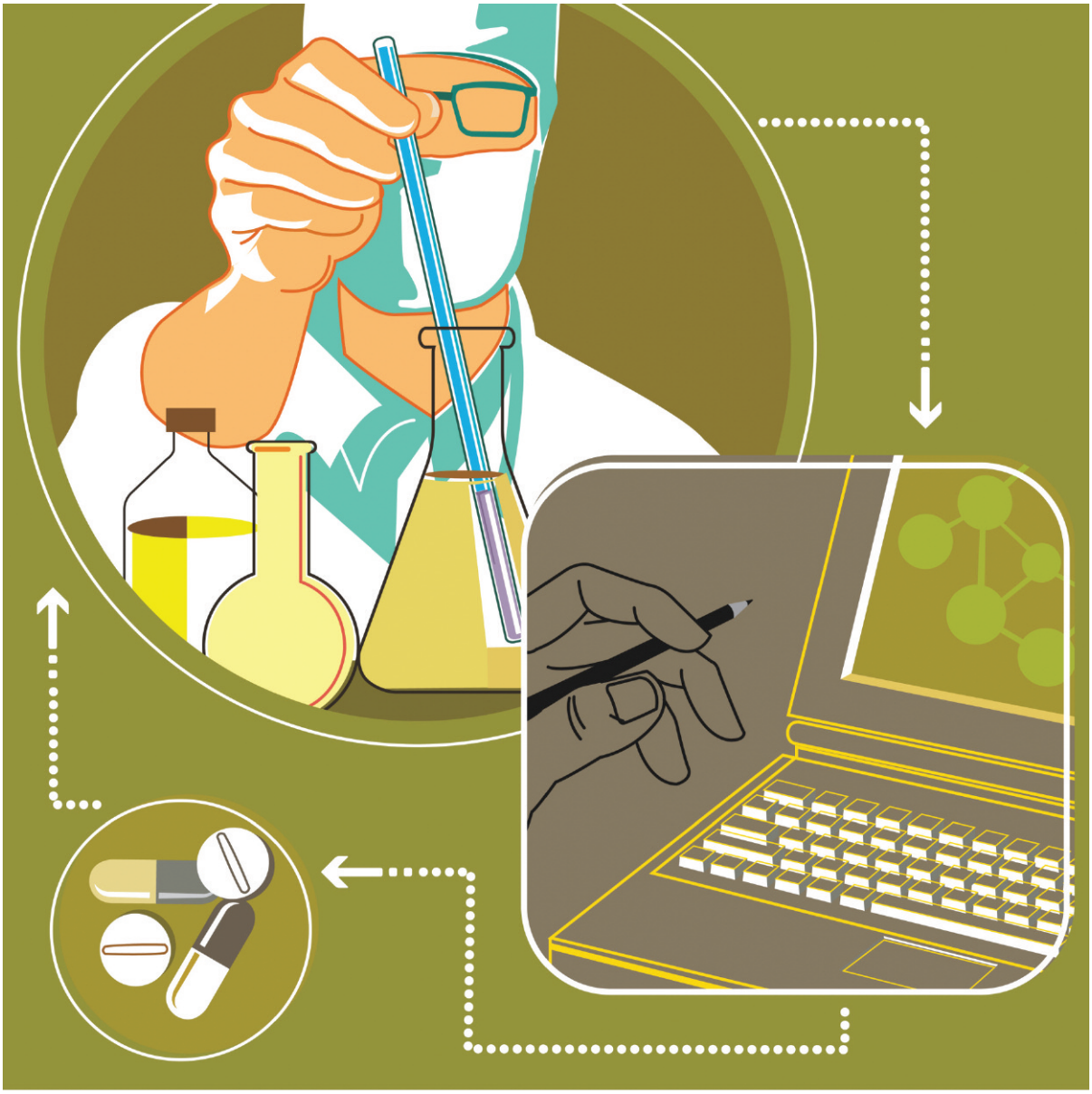
Emerging Therapies for Multiple Sclerosis



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Counseling Points™

Emerging Therapies for Multiple Sclerosis

Continuing Education Information

Target Audience

This educational activity is designed to meet the needs of nurses who treat patients with multiple sclerosis.

Purpose

To meet MS nurses' educational needs on current topics in multiple sclerosis, acknowledging the nurse's role in patient counseling.

Learning Objectives

Upon completion of this educational activity, the participant should be able to:

- Identify newer multiple sclerosis (MS) disease-modifying therapies (DMTs) in review by the Food and Drug Administration or in research phases
- Analyze potential benefits and drawbacks of newer agents as they impact patient care
- Discuss patient issues relating to switching from an established DMT to a newer agent, including safety/tolerability concerns and monitoring issues
- Describe strategies for counseling patients about the newer agents and the importance of starting and maintaining DMTs in MS

Continuing Education Credit

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This activity has been approved for 1.0 contact hours.

Approximate time to complete this activity is 1 hour.

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welcome

Dear Colleague,

Many of us were practicing or studying nursing in the early 1990s when a new drug called interferon beta 1b—and other agents soon to follow—changed the face of multiple sclerosis (MS) as we knew it.

Is anyone else getting a feeling of déjà vu? Again, we perceive a sense of hope and cautious excitement as we review promising efficacy data for newer disease-modifying therapies (DMTs) for MS, many with novel routes of administration quite different from our current injectable therapies.

Are we looking at a true oasis—or just a mirage? Or possibly a little of both? As researchers experiment with monoclonal antibodies, lymphocyte inhibitors, and other new routes to suppressing MS, safety concerns become overriding. How will these agents be tolerated over the long term? Will their benefits outweigh their safety risks? What kind of monitoring will be required? Which patients are the best candidates to try these newer therapies?

At present, we still have more questions than we have answers. We simply need more time to determine how the emerging MS therapies will play out in comparison with our current drugs, which have excellent long-term efficacy and safety profiles extending 10 to 15 years and beyond. We don't have an easy response to give to a patient who is eager to try something new.

Recognizing that this topic is a "moving target," with ever-changing data and information being added, this issue of *Multiple Sclerosis Counseling Points*™ discusses emerging therapies with a view toward the nurse's role in counseling the patient with MS. We hope you find it of interest.

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Emerging Therapies for Multiple Sclerosis

Counseling patients about starting and maintaining a disease-modifying therapy (DMT) for multiple sclerosis (MS) has never been easy—but, until recently, it was somewhat straightforward. The relative efficacy and long-term safety of the conventional or "platform" DMTs have been well established through research data and clinical experience. And the choice of therapies has been limited among a handful of agents: three interferon formulations, glatiramer acetate, and mitoxantrone.

Now, a revolution in DMT for MS is on the horizon. No fewer than a dozen new therapies are in either Phase II or Phase III clinical trials and several agents have been "fast-tracked" by the Food and Drug Administration (FDA) to expedite their consideration for approval in the United States.[1]

What Are the Needs?

Overall, patients receiving the currently available DMTs do significantly better than those on no therapy.[2] They experience reduced lesion activity and brain tissue deterioration on magnetic resonance imaging (MRI) and slower progression to disability. But our patients are individuals—not statistics. For most people, MS eventually progresses over time and for many this progression is not adequately slowed by the existing agents.[2-4] Some patients tolerate the side effects of these drugs fairly well; others have a dramatically reduced quality of life due to adverse effects.[5] Some patients handle the regular injections as part of their routine; others are worn down by the endless shots. Some will reject therapy altogether if it involves regular self-injection. Virtually all patients with MS experience fear, frustration, and doubt, especially with an exacerbation or change in clinical status.

Patients are asking: what else is out there? They are reading about new oral immunomodulators, infused monoclonal antibodies, and other drugs with novel mechanisms. Some of the new agents sound almost too good to be true. But we can't overlook the significant health risks of some agents—risks of a different nature and greater magnitude than we have seen with the beta interferons and glatiramer acetate. As new therapies become commercially available, patients will be looking to the MS nurse to help put their risks and benefits into perspective.

What Do Patients Want?

Earlier this year, results were released from "MS Viewpoints: Understanding the Outlook on Emerging Therapies," an industry-sponsored survey conducted in conjunction with the National MS Society (NMSS).[6] The polling organization interviewed 250 neurologists, 250 health care professionals (drawn from MS centers and the International Organization of MS Nurses [IOMSN] databases), and 250 people with MS. Participants were asked to discuss their perspectives about current treatment options and new therapies in the pipeline. The survey confirmed what MS nurses know anecdotally: patients often delay or decline to start treatment for MS because of the current delivery method of regular injections.

Many MS clinicians believe that with the approval of new therapies for MS—particularly oral therapies—more patients with confirmed MS will come "out of the woodwork" than are currently receiving treatment. Among the NMSS survey's findings:

- 77% of health care professionals and 68% of physicians believe that patients delaying DMT would have started treatment more quickly if oral medications were available.
- 33% of people with MS said their current treatment "interferes with quality of life and daily activities."
- 52% of people with MS said they would consider asking their physician about a newly approved treatment and whether it's right for them.
- 77% of physicians and 74% of health care providers surveyed said they expect to see more requests from patients for specific therapies as new agents become available.[6]

Monoclonal Antibodies by Infusion

Monoclonal antibodies (MABs) are a natural choice for investigation as MS therapies **(Table 1)** because they are designed to recognize specific antigens, the proteins that provoke an immune response.[7] Antibodies (also called immunoglobulins) are blood-borne proteins produced by B cells and plasma cells. Normally, their role in the immune system is to identify and neutralize bacteria or viruses by binding to and recognizing the antigen in the infected cell. In MS, MABs target and reduce or eliminate

Table 1. Monoclonal Antibodies in MS Clinical Studies

Generic Name (Brand Name)	Category	How Administered	Mechanism	Trial Status/ When Completed
Alemtuzumab (Campath®)*	CD52 monoclonal antibody	IV infusion over 3 to 5 days once per year	Depletes circulating B and T cells	CARE-MS: Phase III trial versus Rebif® ends December 2011
Ocrelizumab (2nd generation of rituximab)	CD20 monoclonal antibody	2 IV infusions 2 weeks apart every 6 months	Depletes circulating B cells	Phase II trial versus Avonex® and placebo ends January 2012
Daclizumab (Zenapax®)*	CD5 monoclonal antibody	IV infusion every 4 weeks; SC injection every 4 weeks being tested	IL-2R blockade inhibits T- and B- cell proliferation	Phase II trial (IV form) completed; 1-yr extension of SC formulation trial ongoing, ends December 2012

*Currently approved for non-MS indications.
IV=intravenous, SC=subcutaneous.
Source: www.ClinicalTrials.gov.

selective lymphocytes (such as T cells and/or B cells) in an attempt to prevent some or all of the autoimmune attack on myelin.[7]

Some MAB therapies may require patients to accept a tradeoff: potentially greater efficacy and a less-frequent dosing schedule, coupled with a higher risk for more serious and even potentially fatal side effects.[8] In addition, the long-term effects of depleting these types of immune cells in individuals with MS are unknown.[9]

Alemtuzumab (Campath®)

Alemtuzumab is a MAB targeting CD52, a surface antigen expressed by T cells, B cells, macrophages, and other lymphocytes.[10] This gives it a fairly broad range that may help explain its impressive efficacy results, as some of its lead investigators have speculated.[11] Alemtuzumab has been approved in the United States since 2001 for the treatment of chronic lymphocytic (B-cell) leukemia.[12] In MS, it is administered once yearly by intravenous (IV) infusion over a period of 3 to 5 consecutive days.

One-year results of a Phase II study showed that alemtuzumab reduced the risk of relapse by 74% and accumulation of disability by 71% ($P<0.0001$ for both) compared with subcutaneous (SC) interferon (44 mcg 3x/week).[13] Two-year results reported at this year's American Academy of Neurology (AAN) meeting showed that 41.5% of patients attained sustained reduction in disability compared with 26.9% of patients taking interferon.[14]

An interesting finding reported at that meeting was that alemtuzumab appears to provide sustained protection against disability and relapse for at least 24 months after the last dose of the drug.[15] The mechanisms of these "durable effects" are under investigation. In addition, over 50% of the alemtuzumab-treated patients in the 1-year study showed improvements in measures of disability, suggesting a potential neuroprotective effect of the drug that warrants further study.[16]

Side effects of alemtuzumab include a disruption in blood clotting, infusion reactions, and infection **(Table 2)**. Patients need to be monitored closely due to the risk of toxicities such as immune thrombocytopenic purpura

Table 2. Monoclonal Antibody Adverse Events Observed in MS Clinical Trials

Alemtuzumab (Campath®)

- Immune thrombocytopenic purpura (ITP)
- Thyroid AEs, including hyper- and hypothyroidism
- Infections: gastroenteritis, bronchitis, cellulitis, cervicitis, Listeria meningitis, viral meningitis, urinary tract infection, primary varicella
- Infusion-related AEs, including infusion reaction, abnormal liver function, bradycardia, hypertension

Rituximab (Rituxan®)

- Fever, rigors, tachycardia, dyspnea, headache, pruritis, rash
- Serious AEs: progressive multifocal leukoencephalopathy (PML) has been reported in patients taking rituximab for other diseases such as rheumatoid arthritis and lupus

Daclizumab (Zenapax®)

- Cutaneous reactions
- Possibly increased severity of common infections
- Serious AEs: None reported

AEs=adverse events.

(ITP), which occurred in six of 216 patients in the published 1-year study (versus one interferon-treated patient). Because alemtuzumab also inhibits suppressor (regulatory) T cells, high rates of secondary autoimmune disorders such as thyroid disease have been observed in people receiving the drug.[17]

A Phase III study of alemtuzumab, CARE-MS, will enroll 525 treatment-naïve patients with relapsing-remitting MS (RRMS) and will use SC interferon beta-1a (44 mcg) as a comparator. The expected completion date for this trial is December 2011.[18]

Rituximab (Rituxan®) and Ocrelizumab

Rituximab is currently approved for use in non-Hodgkin's lymphoma and rheumatoid arthritis.[19] This MAB binds to CD20, a surface antigen on B cells, causing temporary depletion of B cells for approximately 9 months. A multicenter Phase II double-blind study in MS evaluated a single course of treatment (two infusions administered 2 weeks apart), and showed a 91% reduction in active lesions and a 58% reduction in relapses at 24 weeks compared with placebo.[20] The effect was sustained at 48 weeks. Gadolinium-enhancing (GdE) lesion inhibition on MRI was seen as early as week 12.

Most adverse events in the Phase II studies of rituximab were believed to be associated with B-cell depletion, and included fever, rigors, tachycardia, dyspnea, headache, pruritis, and rash.[20] In addition, B-cell depletion increases the risk of opportunistic infections. Experience with other diseases has shown that, as with natalizumab, rituximab treatment carries a risk of progressive multifocal leukoencephalopathy (PML), which requires close monitoring of patients.[19]

Anyone following the research on rituximab, which has been abandoned as a research target in MS, should become familiar with the name "ocrelizumab," because all further clinical studies in MS will be done using this humanized MAB, which is a second-generation of ritixumab. This decision was made because antichimeric antibodies found in patients with MS after rituximab treatment were thought to potentially complicate repeat administrations. An ongoing Phase II study will compare two ocrelizumab doses with intramuscular (IM) beta interferon over 6 months in patients with RRMS.[21]

Daclizumab (Zenapax®)

Another FDA-approved MAB being tested in MS is daclizumab, currently used to treat acute renal allograft rejection. Daclizumab binds to interleukin 2 (IL-2) and causes T-cell and B-cell depletion.[22] Compared with the other MABs discussed, daclizumab has a more frequent dosing schedule (via IV infusion every 4 weeks or SC injection every 2 weeks), with a rapid loss of efficacy when treatment is discontinued. In the multicenter Phase II CHOICE study of SC daclizumab in patients with treatment-refractory MS, a 72% reduction was seen in the number of GdE lesions at 6 months, although the secondary outcome of change in relapse rate was not significant.[23] All subjects remained on interferon therapy during this study.

To date, daclizumab appears to have a better safety profile than some other MABs. In the Phase II trials, cutaneous reactions and "possibly increased severity" of common infections were the most common adverse events. No opportunistic infections, malignancies, or autoimmune phenomena were observed.[23] However, as with any of these agents, more long-term data are needed to better evaluate the safety of this agent in MS.

An ongoing Phase II trial will evaluate daclizumab monotherapy (SC injection every 2 weeks) versus placebo for 48 weeks.[24]

Oral Agents for MS

If you've ever had a patient ask why there are no oral DMTs for MS, that conversation may soon be behind you. Several oral agents for MS are now in Phase II or III studies, five of which are discussed here **(Table 3)**. Oral administration is by far the preferred route because of its ease for both patients and prescribers.[25] Some oral agents are administered just a few times per year. However, if their safety risks entail close monitoring, the need for regular blood tests could balance out some of their convenience **(Table 4).**

Cladribine

Cladribine is an oral drug that was recently submitted to the FDA for an MS indication. It is a synthetic cytotoxic immunomodulator that depletes T lymphocytes by causing apoptosis. Parenterally administered cladribine (Leustatin®) is currently approved for treating hairy cell leukemia.[26] Promising results from early studies with IV cladribine in MS (including dramatic 90% reductions in GdE lesions) led to the development of the oral version for MS.[27] Phase III trials recently concluded, with preliminary findings reported at the 2009 AAN meeting.[28]

In the Phase III CLARITY trials, oral cladribine was given in 5-day cycles either 2 or 4 times per year and compared with placebo in 1,326 patients with early RRMS.[28] The cladribine dosage was weight-dependent, with the

Table 3. Oral Agents in MS Clinical Studies

Generic Name (Brand Name)	Category	How Administered	Mechanism	Trial Status/ When Completed
Cladribine* (FT)	Immunomodulator	Oral; 2 courses per year of 1 tablet per day for 4 or 5 days	Selectively depletes CD4 T cells	CLARITY: Phase III versus placebo, completed ONWARD: Phase II trial ends November 2013 ORACLE: Phase III study ends December 2012
Fingolimod	Immunomodulator	Oral once daily	Blocks T-cell release and proliferation	FREEDOMS: Phase III trial versus placebo ongoing TRANSFORMS: Phase III trial versus Avonex® completed
Laquinimod (FT)	Immunomodulator	Oral once daily	Reduces infiltration of CD4 and CD8 T cells, and macrophages	ALLEGRO: Phase III trial versus placebo ends 2010 BRAVO: Phase III trial versus Avonex®, ends November 2011
BG00012 (also Dimethyl Fumarate) (FT)	Immunomodulator	Oral, daily; 3 dosage strengths being tested	Activates Nrf2 pathway to reduce oxidative stress	DEFINE: Phase III study, 2 doses versus placebo ends December 2010 CONFIRM: 2 doses versus Copaxone® and placebo ends April 2011
Teriflunomide	Immunomodulator	Oral daily	Affects T-cell division	TEMSO: Phase III trial versus placebo ends October 2010 TENERE: Phase III study versus Rebif® ends October 2011 TOPIC: Phase III trial versus placebo ends October 2012

*Currently approved for non-MS indications.
FT=granted "fast track" status by the FDA.
Source: www.ClinicalTrials.gov.

best results seen with 3.5 mg/kg. The optimal dosage regimen has yet to be determined, investigators say.[29] Patients receiving cladribine were 55% less likely to experience relapse and 30% less likely to have an increase in disability during the study period compared with placebo.

In trials of IV cladribine in MS, the most common adverse events were cytopenia, infections (upper respiratory tract, urinary tract, herpes zoster), muscle weakness, purpura, injection-site reactions, hypertonia, and back pain.[27] In the CLARITY trial of oral cladribine, the most common treatment-emergent adverse event was lymphopenia, which occurred in 22% of patients receiving 3.5 mg/kg (versus <2% in the placebo group).[29]

Long-term safety remains an important question with cladribine. Because it is a cytotoxic agent that interferes with DNA processing, the reproductive implications must be considered for both male and female patients. Another consideration may be the risk of malignancies, which were observed in the CLARITY trial among four users of cladribine.

An ongoing Phase II study, ONWARD, involves patients with RRMS who had at least one relapse while on interferon therapy. A group receiving combination oral cladribine and a titrated form of SC interferon beta is being compared with a group receiving interferon alone.[30] A Phase III trial in progress, ORACLE, involves patients with clinically isolated syndrome (CIS) and compares two cladribine doses (3.5 mg/kg/year and a lower dose) with placebo.[31]

Fingolimod

Fingolimod is a daily oral immunomodulator that acts by sequestering lymphocytes in peripheral lymph nodes.[32] Fingolimod administration rapidly decreases circulating lymphocytes by approximately 70%; this effect is reversible after the drug is discontinued.

Table 4. Oral Immunomodulator Adverse Events Observed in MS Clinical Trials

Cladribine

- Lymphopenia, cytopenia
- Infections: upper respiratory tract, urinary tract, herpes zoster
- Muscle weakness, purpura, hypertonia, back pain
- Serious AEs: malignancies, serious herpes infections

Fingolimod

- Hypertension, airway obstruction, infection, macular edema
- Nasopharyngitis, dyspnea, headache, diarrhea, nausea, asymptomatic liver enzyme elevations
- Serious AEs: malignancies, serious herpes infections, bradycardia or AV block

Laquinimod

- Elevation of liver enzymes
- Serious adverse events: 1 case of Budd-Chiarri syndrome (thrombotic venous outflow liver obstruction) in patient with underlying hypercoagulability (Factor V Leiden mutation)

BG0012 (Dimethyl Fumarate)

- Gastrointestinal symptoms: nausea, abdominal pain, vomiting, diarrhea
- Headache, fatigue, flushing sensation (dose-dependent)
- Serious AEs: None reported

Teriflunomide

- Possible teratogenic effects
- Nasopharyngitis, alopecia, limb pain, arthralgia, nausea
- Serious AEs: Hepatic necrosis and pancytopenia have been observed in patients taking teriflunomide for rheumatoid arthritis

AEs=adverse events, AV=atrioventricular

In a 6-month, Phase II study versus placebo, oral fingolimod reduced the annualized relapse rate by more than 50% and the cumulative number of GdE lesions by up to 80%.[33] After 24 months, 79% in the treatment group remained free of GdE lesions and 77% remained relapse free.[34] A 36-month Phase II study showed that 60% of patients with RRMS remained relapse-free.[35]

Twelve-month data from the Phase III TRANSFORMS trial comparing oral fingolimod with IM interferon beta-1a in RRMS were presented at this year's AAN meeting.[36] In this trial, patients receiving fingolimod 0.5 mg/day had superior outcomes at 12 months compared with those receiving IM interferon, with a lower annualized relapse rate (0.16 versus 0.33; P=0.001) and fewer GdE lesions, and a greater percentage of patients being relapse free (83% versus 69%; P=0.0001).

Adverse events associated with fingolimod may include bradycardia, hypertension, airway obstructions, infection, and increased intraocular pressure. Events reported in Phase II clinical trials of fingolimod included nasopharyngitis, dyspnea, headache, diarrhea, nausea, and asymptomatic liver enzyme elevations.[34,35] In the TRANSFORMS trial, serious adverse events included 12 malignancies (versus two for interferon), two fatal herpes infections (zero for interferon), and bradycardia or AV block (20 versus zero for interferon).[36]

As with many agents, extensive monitoring for safety risks will be needed if fingolimod is approved for the treatment of MS (a New Drug Application is expected to be filed shortly). Because of the potential for cardiopulmonary effects, extensive post-dose monitoring, including regular electrocardiograms, may be required at the start of treatment.[37]

Laquinimod

Laquinimod is another oral daily immunomodulator for MS currently in Phase II and III trials. Laquinimod is a derivative of linomide, restructured to reduce adverse effects.[38]

Its primary mechanism is to modulate cytokine balance in favor of anti-inflammatory Th2/Th3 cytokines. In addition, this agent has been shown to increase levels of neurotrophic factors (BDNF) in vivo, potentially conferring a neuroprotective effect.

In a 36-week Phase II trial, laquinimod 0.6 mg/day resulted in a 40% reduction in mean cumulative GdE lesions per scan versus placebo (P=0.0048). Patients in the laquinimod 0.6 mg group also had 44% fewer cumulative new T2 lesions and 51% fewer T1 hypointense lesions compared with those receiving placebo.[39] A 36-week extension of this study re-randomized patients in the placebo group to receive one of two laquinimod doses.[40] Those switching to active treatment had a 52% reduction in GdE lesions (P<0.0007), while 47% of those starting on the active therapy did not develop new lesions.

In these trials, laquinimod appeared to be well-tolerated, with the main safety concern being self-limited, dose-dependent increases in liver enzymes observed in Phase II studies.[39] No clinical evidence of a proinflammatory effect was seen. There was no evidence of the cardiopulmonary effects associated with its predecessor.[41]

The 24-month BRAVO study comparing laquinimod and IM interferon beta is currently in the recruitment stage, while the ALLEGRO trial compares laquinimod with placebo in patients with RRMS.[42,43]

Dimethyl Fumarate (also called BG12 or BG 00012)

This drug is related to fumaric acid, a substance commonly used to treat psoriasis. This second-generation oral fumarate derivative was developed to improve tolerability.[44] In MS, it acts as an immunomodulator, partly by suppressing oxidative stress-induced neuronal death. Fumarate is administered daily. This agent has been granted fast-track status by the FDA.

In a Phase IIb dose-ranging study versus placebo, the highest dose of fumarate reduced new GdE lesions between weeks 12 and 24 by 69%, the relapse rate by 58%, and new or enlarging T2 lesions.[45]

Dimethyl fumarate has been relatively well tolerated in clinical trials. Predominant side effects have included gastrointestinal (GI) symptoms (nausea, abdominal pain, vomiting, and diarrhea), along with headache, fatigue, and a flushing sensation, some of which were found to be dose-dependent.[45]

Phase III trials of fumarate in MS are in the recruitment phase. These include DEFINE, a dose-finding study versus placebo in approximately 1,000 patients, and CONFIRM, which compares two fumarate doses with either glatiramer acetate or placebo in 1,232 patients.[46,47]

Teriflunomide

Another daily oral immunomodulator in the early stages of study, teriflunomide is the active metabolite of leflunomide, which is used to treat rheumatoid arthritis. Teriflunomide acts in MS by decreasing T-cell and B-cell proliferation.[48] This drug has been studied in both RRMS and secondary progressive MS (SPMS) in a Phase II study with a primary endpoint of unique lesions per scan, which were reduced versus placebo. The treatment also reduced GdE lesions and T2 lesions.[49]

Teratogenicity observed in animal studies has led to the recommendation for both women and men to avoid conception during treatment and possibly for a prolonged period after treatment.[44] Other safety issues include adverse effects of nasopharyngitis, alopecia, nausea, limb pain, and arthralgia. Some patients with rheumatoid arthritis taking teriflunomide have developed hepatic necrosis and pancytopenia.[44]

Two Phase II combination studies are in progress—one of teriflunomide added to interferon beta; the other adding it to glatiramer acetate. Both will evaluate tolerability and safety, the number of gadolinium-enhancing lesions, and burden of disease on MRI.[50,51]

A 2-year Phase III study is recruiting participants who have had a first episode (CIS) consistent with MS. Its primary outcome measure is conversion to clinically definite MS (CDMS). Secondary measures include relapse rate, burden of disease and other MRI variables, and the proportion of patients who remain free of disability.[52] Other Phase III studies are being conducted in patients with RRMS and with a first clinical episode of MS (TOPIC).[53]

Large Volume of Ongoing Research

By one estimate, there are more than 136 ongoing clinical trials for MS drugs, most of which involve newer agents.[54] In addition to the MABs and oral immunomodulators discussed here, studies are being conducted with statins, estriol, and the antibiotic minocycline, to name a few other agents.[44] The sheer number of trials and the pace at which research is proceeding offers much hope for people with MS, including those with progressive forms of the disease. It also raises the challenge of finding patient populations appropriate to test these agents, especially when the studies progress to larger Phase III trials.

Safety Risks and Monitoring: Lessons Learned From Natalizumab (Tysabri®)

The introduction of natalizumab set the stage for the MABs in MS. Administered by once-monthly infusion, natalizumab entered the market in 2004 following an expedited "fast track" review by the FDA. The drug was voluntarily withdrawn in February 2005 after some MS patients developed PML, a frequently fatal viral infection of the brain. Natalizumab was re-released in June 2006 with some safety precautions in place and limiting prescription to qualified health care providers who are enrolled in the TOUCH Prescriber Program.[55] In November 2009, Tysabri® labeling was updated to include a statement that the risk of PML increases with longer usage of the drug. Patients treated for 24 to 36 months have a risk of PML occurrence of about 1 in 1,000. Beyond 3 years, however, there is little experience with the drug.

Some of the lessons learned from natalizumab's rocky start on the MS market may be applicable to new therapies. Requirements for certified prescribers and other restrictions regarding who can dispense and receive certain drugs may be part of the future as more novel MS drugs are introduced. Such restrictions increase the likelihood that prescribers and patients will be fully informed about the risks of these agents and will follow through with monitoring necessary to prevent or reverse serious adverse effects, when possible.

Monitoring and Administration: New Complexities

Even with the current so-called platform DMTs, monitoring patients for reversible adverse effects has been a challenge. For example, patients receiving beta interferon for MS are advised to undergo regular monitoring, which includes complete blood count (CBC) and differential white blood cell counts, platelet counts, and blood chemistries, and tests for liver and thyroid function. Many MS clinicians will acknowledge that adherence to this monitoring is low. Recently, some insurance companies have begun to require copies of laboratory results to verify monitoring before they will authorize payment for an interferon prescription.

Such strategies may help increase vigilance over patients on the new drugs. However, a unique aspect of some new MS drugs is the wide dosage interval—oral agents like cladribine or infused drugs such as alemtuzumab may be administered as infrequently as once per year. In these cases, restricting prescribers would not solve the problem of maintaining adherence to monitoring after the drug has been given. Withholding refills is also obviously a less effective strategy for keeping track of patient status than it would be with a more frequently dosed drug.

Assuming that some new therapies will become part of the standard of care in MS, many of our nursing practices will eventually need to be modified. New best practices for monitoring and modes of administration will need to be established either in the office or clinic, or when possible in existing facilities such as infusion centers. Billing arrangements will need to be modified in light of the costs of medical and nursing time, monitoring, and provider and patient education.

Patient Education: Venturing Into the Unknown

Educating patients about the basics of MS—what it is, why treatment is necessary, how the disease progresses differently in everyone—is a key challenge for the MS nurse. That job will most likely become much more challenging in the future. Explaining the different mechanisms of the new therapies will require fairly sophisticated knowledge about the immunology behind the disease. Nurses will need to help patients establish reasonable expectations for these agents, their methods of administration, need for safety monitoring, and potential side effects.

It is reasonable to assume that an increased variety of options, while a positive step overall, will prolong the time needed for patient counseling, especially for newly diagnosed patients. Yet, in the current health care environment, clinicians are already facing many obstacles to spending time with patients. High-quality and well-balanced patient education materials, developed in consultation with MS nursing professionals, will be needed to help clarify and streamline this process.

The nursing process for a new patient, or any patient, might be described as "dynamic therapeutics." This means looking at each patient with new eyes, each time he or she comes in for a consultation. It means taking into consideration any changes in the patient's medical condition, priorities and lifestyle, age and living arrangements, and family planning status. This approach would apply whether a patient is newly diagnosed, has been on a platform therapy for many years, or is considering treatment for the first time.

Long-Term Safety: The Biggest Unknown

With any new drug for MS, long-term safety is always going to be in question until more clinical experience can be obtained. Although oral drugs for MS have been in demand for some time, their potential safety risks with only 2 years' data must be weighed against the 10- to 15-year safety records established with the current DMTs. We cannot take hope away from patients, but we do have to be transparent about the potential risks and make it clear to patients that we don't have all the answers.

PML has been one of the most significant and frightening concerns. According to recent reports, 23 new cases of PML have been identified since natalizumab went back on the market, an incidence of about 1 in 1,000 patients.[56] We still don't know why some patients taking natalizumab develop this illness. Symptoms often don't appear until the patient has received many doses of the drug—in some cases, after 12 or 14 doses. Another recently published study showed that MS patients taking natalizumab may have elevated urine and blood levels of the JC virus, which causes PML.[57] The implications of this finding are still unclear, though, since about one-third of healthy adults are thought to carry dormant JC virus without developing PML.[57]

The effect of switching among therapies or combining therapies is another area where no roadmap exists. We don't know the impact on the patient of starting and

stopping some of these agents. Some have a treatment effect of a year or more, unlike other therapeutic areas in which alternative drugs can be more easily substituted.

Another question that remains to be answered: which therapies may be best for which patients? Patient selection for a higher-risk therapy may be made, in part, based on the individual's understanding of the risks and his or her commitment to partnering with the health care team to maximize safety.

At this stage, it is also impossible to make far-reaching statements about the efficacy of these agents, especially those studied mainly in Phase II trials. Because of their smaller sample size, Phase II studies do not have sufficient power to evaluate the effects of DMTs on clinical outcomes (such as relapse rate and change in disability), according to Jana Preiningerova of the Yale MS Center.[41] Thus they must use "surrogate outcomes" (eg, MRI) to determine the therapeutic potential of new drugs. Dr. Preiningerova added that predicting clinical efficacy of new drugs based on MRI outcomes (such as number of GdE lesions) may be "misleading" if the drug's mechanism does not target the blood:brain barrier.

Should Patients on Platform Therapies Switch?

For patients who are doing well on their current therapy, is newer necessarily better? For many of these patients, a "watch and wait" approach may be the most prudent. Only time, long-term comparative studies, and postmarketing experience can elicit which of these new agents are safe, effective, and well tolerated for MS patients in the community setting, outside of stringent clinical trial protocols.

To determine whether a patient is "doing well," three variables need to be addressed: efficacy, safety, and tolerability. If there are problems with any of these three, other options might be considered. Remember that while the nurse's order of priority might be safety, efficacy, and tolerability, the patient's might be tolerability, efficacy, and safety. Tolerability includes injection fatigue, which is a reality for many of our MS patients.[58] The nurse may need to help the patient put this in perspective relative to the potential complications of newer agents, many with as-yet unknown effects. Having to self-inject and manage injection-site reactions are not desirable, but they may in fact look more tolerable in view of the side effects of other therapies.

The higher complexities of care demanded with new therapies emphasizes the key role of the MS nurse specialist in patient and provider education, and the importance of keeping abreast of this complex and constantly changing practice environment.

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- Currently, over a dozen promising new disease-modifying therapies (DMTs) are in Phase II and/or Phase III clinical trials for multiple sclerosis (MS).
- Some of the new therapies are monoclonal antibodies given by intravenous infusion. Monoclonal antibodies such as alemtuzumab have had impressive efficacy results in trials thus far, but carry greater potential risks than current injectable drugs.
- A number of oral therapies are being studied in MS and a few have been or will soon be submitted for FDA "fast track" approval.
- Cladribine and fingolimod are oral therapies with Phase III trial data available. These agents may be associated with more potentially serious adverse effects, including malignancies and infections, than the currently available "platform" therapies.
- Other oral therapies in earlier stages of study, including laquinimod, dimethyl fumarate (BG00012), and teriflunomide, may offer a better safety profile than cladribine and fingolimod because of the lack of infections, malignances, and other serious adverse events observed in clinical trials.
- The experience with natalizumab and the associated incidence of progressive multifocal leukoencephalopathy (PML) has been a "wake-up call" to the potential risks of new therapies. There are now tighter restrictions for prescribing and receiving this drug, but it is still not possible to predict which patients might develop PML during natalizumab therapy.
- The availability of a greater variety of therapies will increase the complexity of care in MS, in terms of helping patients make therapeutic selections, administration, monitoring, patient education, and adherence.

Counseling Points™
Emerging Therapies for Multiple Sclerosis

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Via the Web: Applicants can access this program at the International Organization of MS Nurses' website, www.IOMSN.org. Click on Counseling Points and follow the instructions to complete the online posttest and application forms.

PLEASE SELECT THE BEST ANSWER

1. **Drawbacks of currently approved disease-modifying therapies (DMTs) used for multiple sclerosis (MS) include all of the following EXCEPT:**
   A. need to self-inject
   B. adverse events that affect quality of life
   C. lack of long-term safety data
   D. disease progression despite therapy

2. **True or false? The majority of MS health care professionals responding to a National Multiple Sclerosis Society (NMSS)-sponsored survey believe that patients who delay starting DMTs would start earlier if oral agents were available.**
   A. True
   B. False

3. **The mechanism of action of monoclonal antibodies in MS is to target and eliminate or reduce:**
   A. red blood cells
   B. myelin basic protein
   C. lymphocytes
   D. all of the above

4. **Serious adverse events observed in clinical trials of alemtuzumab included:**
   A. chronic lymphocytic leukemia
   B. immune thrombocytopenic purpura (ITP)
   C. progressive multifocal leukoencephalopathy (PML)
   D. none of the above

5. **Ongoing clinical trials for rituximab in MS will instead go forward using the rituximab derivative called:**
   A. alemtuzumab
   B. daclizumab
   C. natalizumab
   D. ocrelizumab

6. **Among the following oral immunomodulators under study for use in MS, all are administered daily EXCEPT:**
   A. cladribine
   B. laquinimod
   C. ingolimod
   D. teriflunomide

7. **The TOUCH Prescribing Program limits prescription of natalizumab to:**
   A. neurologists or oncologists only
   B. MS nurse specialists and neurologists
   C. MS Care Centers
   D. qualified prescribers enrolled in the program

8. **Requiring laboratory results before refilling a prescription would not effectively induce patients to adhere to safety monitoring while on the oral investigational agent cladribine because:**
   A. pharmacies bypass these requirements
   B. the drug has a wide dosage interval (e.g., once or twice yearly)
   C. the drug is available to patients through clinical trials
   D. none of the above

9. **Testing for antibodies to the JC virus in monoclonal antibody-treated patients with MS is not an effective way to determine which patients may be at risk for developing PML because:**
   A. the tests are sophisticated and expensive
   B. asymptomatic JC infection is common in this population
   C. there is a weak correlation between JC virus and the development of PML
   D. most MS patients are resistant to the virus

10. **In the context of MS nursing, the term "dynamic therapeutics" refers to the process of:**
    A. changing patients' therapies if they request a new treatment option
    B. maintaining patients on a current therapy if the nurse determines they are doing well
    C. looking at patients with "new eyes" at each visit to accommodate changes in clinical status, emotional status, and environment
    D. none of the above

Counseling Points™: Program Evaluation Form

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Using the scale provided, Strongly Agree = 5 and Strongly Disagree = 1, please complete the program evaluation so that we may continue to provide you with high quality educational programming. Please fax this form to **(201)612-8282**.

5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

At the end of this program, I was able to: *(Please circle the appropriate number on the scale.)*

1. Identify newer multiple sclerosis (MS) disease-modifying therapies (DMTs) in review by the Food and Drug Administration or in research phases 5 4 3 2 1
2. Analyze potential benefits and drawbacks of newer agents as they impact patient care 5 4 3 2 1
3. Discuss patient issues relating to switching from an established DMT to a newer agent, including safety/tolerability concerns and monitoring issues 5 4 3 2 1
4. Describe strategies for counseling patients about the newer agents and the importance of starting and maintaining DMTs in MS. 5 4 3 2 1

To what extent was the content…

5. Well-organized and clearly presented 5 4 3 2 1
6. Current and relevant to your area of professional interest 5 4 3 2 1
7. Free of commercial bias 5 4 3 2 1

General Comments

8. As a result of this continuing education activity (check only one):

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_____

❒ I will wait for more information before modifying my practice.

❒ The program reinforces my current practice.

Suggestions for future topics/additional comments:_____

_____

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