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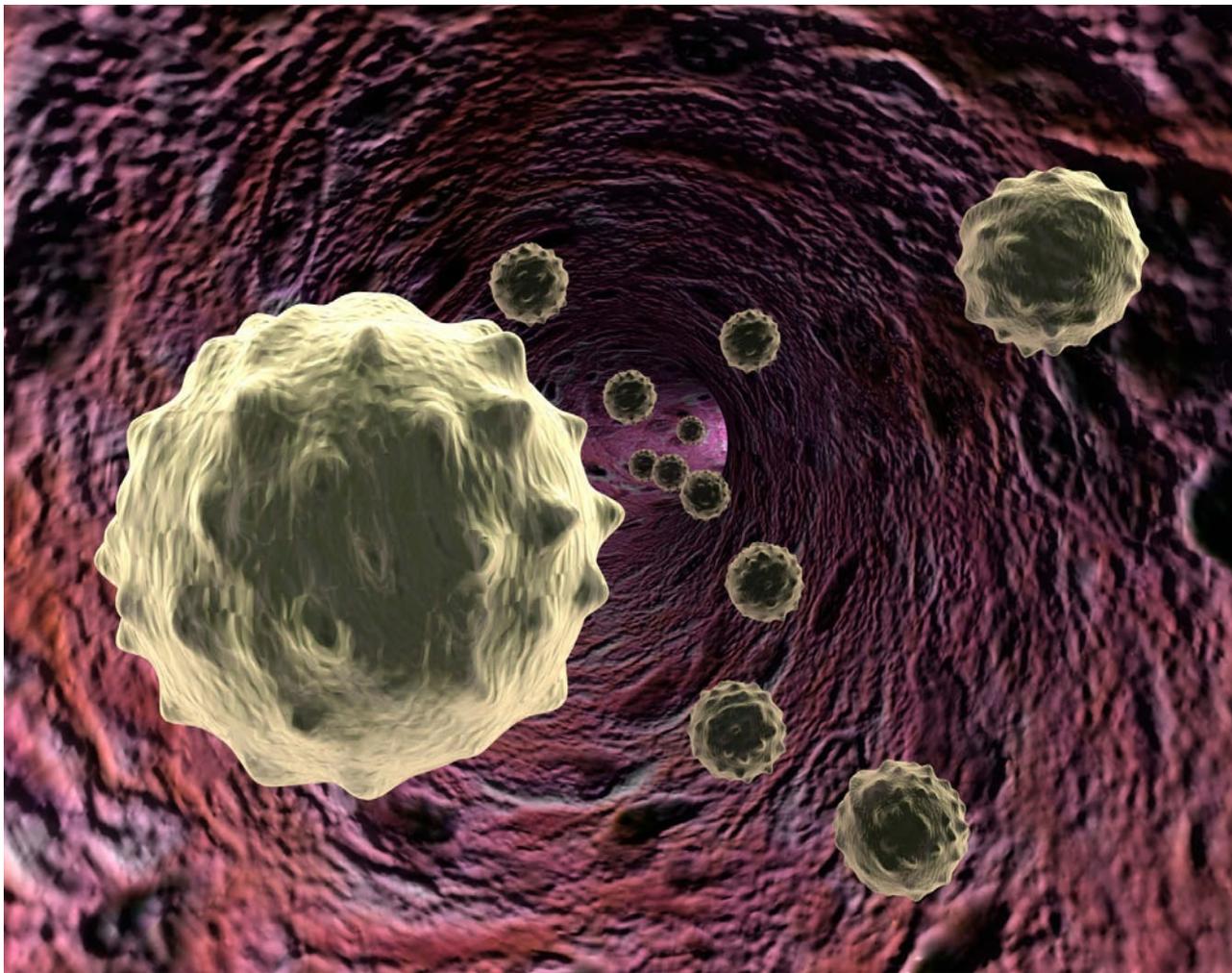
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Modifying the Immune System in MS: What We Know, What We're Learning



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Counseling Points™

Modifying the Immune System in MS: What We Know, What We're Learning

Continuing Education Information

Target Audience

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

Purpose

To provide MS nurses with information needed to perform a risk-benefit analysis for selection of disease-modifying therapies and counsel patients on the potential safety risks of existing and newer medications for MS.

Learning Objectives

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

- Discuss immunomodulation in the context of the current first-line medications available for multiple sclerosis (MS)
- Describe categories of investigational drugs for MS and how their mechanisms may contribute to immunosuppression
- Evaluate risks associated with immunosuppression in MS
- Identify issues for discussion with patients with MS in the selection of appropriate disease-modifying therapies

Continuing Education Credit

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welcome

Dear Colleague,

With the recent introduction of the first oral disease-modifying medication (fingolimod) and several others in the pipeline, a new era of multiple sclerosis (MS) treatment has officially begun. Much hope is riding on the new wave of medications to help manage the disease in people not well controlled on the standard therapies, and to offer an alternative to injected agents.

The newer medications under investigation for MS work by different mechanisms than the existing therapies, and some are considered “immunosuppressants” rather than “immunomodulators,” because they deplete immune cells to a greater degree than do glatiramer acetate or the beta interferons. Thus, they may be associated with greater safety risks, such as infections or malignancies, which may accompany immunosuppression.

As we did during the early years of using the original “platform” therapies, MS clinicians will be watching closely to discover answers to the many remaining “unknowns.” Will fingolimod and its successors be safe for long-term use? How will these oral drugs compare with standard therapies—and with each other—from a safety and efficacy standpoint? Are there some patients for whom the risks outweigh the benefits, and if so, how can we identify these individuals?

MS nurses have a primary role in educating patients and families about new advances in disease management. This issue of *MS Counseling Points*[™] explores the issue of immunosuppression and immunomodulation and what this means for our patients with MS in the current era of disease modification.



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Modifying the Immune System in MS: What We Know, What We're Learning

What is the difference between *modifying* the immune system and *suppressing* it, and what does this difference mean for the safety and efficacy of multiple sclerosis (MS) medications? The standard disease-modifying therapies (DMTs) for MS (“platform therapies”) are generally regarded as *immunomodulators*. They modify the immune system in a variety of ways, such as altering the function of immune cells, preventing activation of immune cells, and protecting the blood:brain barrier (BBB). They do not radically suppress the immune system by eliminating large populations of white blood cells, as do many chemotherapy drugs, stem cell treatments, and some of the newer MS drugs. Not all MS experts agree on which drugs suppress immune function and which modify it—often the line is blurred between these two concepts.

T and B Cells: Key Components of the Immune System

In the normal immune system, white blood cells (leukocytes) are mobilized to fight off foreign invaders such as infections. Among the leukocyte population are the lymphocytes, which include T and B cells important in the pathology of MS (Figure 1). The subtypes listed are just a few of the many known types of T and B cells.

T and B lymphocytes originate in the bone marrow—T cells mature in the thymus and B cells mature in the marrow itself. When the body senses an invader, immune cells are recruited and travel via the bloodstream to the site. Cellular changes may occur causing them to become activated or to differentiate into subtypes (e.g., helper or regulatory T cells) or other cell types. This can affect their behavior in relation to the invader and other types of cells.¹

The Immune System and the Pathology of MS

Antigens are substances that stimulate an immune response in the body. These molecules bind specifically to an antibody or to a T-cell receptor. T lymphocytes have receptors that recognize specific antigens and bind with them. Antigens can be triggered by a foreign substance but also by the body's own cells. In a healthy state, the “self” antigens are tolerated by the immune system while outsider antigens (say, from a virus) are identified as intruders and attacked.¹ In MS, however, the immune system reacts to its own antigens by sending out lymphocytes to attack. The main focus of the attack is myelin, the coating surrounding nerve fibers in the central nervous system (CNS) and the axons. The exact antigen, or target, that sensitizes the immune cells to attack myelin remains unknown.²

Although autoimmunity in MS was long believed to be driven mainly by T cells, recent research has shown that the process is likely to be an interplay between the two types of lymphocytes (T and B cells) (Table 1).³⁻⁵

Targets for Modulating or Suppressing the Immune System

Ideally, one could fully interrupt or reverse the immune dysfunction causing damage in MS while

Figure 1. White Blood Cell “Family Tree”

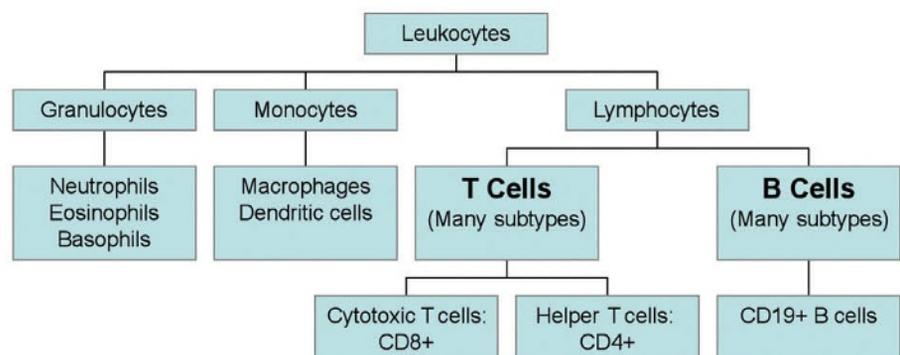


Table 1. Proposed Roles of B Cells in MS³

B cells are thought to:

- Efficiently present antigens to T cells
- Cause activation of naïve T cells to induce secretion of pro-inflammatory substances
- “Prime” autoreactive T cells
- Become activated and induce production of T-cell-secreted cytokines
- When activated, convert to plasma cells that secrete antibodies, bind complement, and contribute to tissue destruction

leaving the rest of the immune system intact to carry on its normal functioning. Unfortunately, such a precise “magic bullet” for MS has yet to be discovered.

The term *immunosuppressant* is applied to drugs that lower the body’s immune response to invasion by a “foreign” substance. Immunosuppressants for MS work primarily by depleting or suppressing the function or movement of large populations of lymphocytes (T and B cells). In doing so, these agents also have the tendency to lower the body’s immune response to infection by opportunistic organisms (those that proliferate in a weakened immune environment).^{6,7}

Immunomodulators interfere with portions of the immune process and leave other parts intact to fight off infections. Many MS therapies interrupt various steps involved in inflammation and the immune attack on myelin by modifying the behavior of the immune cells (**Table 2**). In order to damage the CNS, the

Table 2. Mechanisms for Immunomodulation and Immunosuppression in MS

MS drugs suppress or modulate the immune system by various pathways, such as:

- Depleting T and B cells in the bone marrow
- Inhibiting T and/or B cells from being recruited out of the bone marrow
- Preventing immune cells from becoming activated in the circulation
- Preventing inflammatory cells from crossing the BBB into the CNS
- Modifying inflammatory cells’ function in the CNS (e.g., changing the inflammatory cells’ purpose from “cytotoxic” or damaging types of cells to “regulatory” types of T cells)
- Interfering with antigen function

CNS=central nervous system.

immune cells must cross the BBB, a cellular barrier in the bloodstream that protects the brain and nervous system. Interfering with the immune cells’ ability to cross the BBB is an important mechanism of many MS immunomodulators.

Mechanisms of Action of MS “Platform” Therapies

Interferons

Recombinant interferon agents were the first DMTs introduced for MS. Interferons are naturally occurring proteins in the body that are released by the lymphocytes in response to a pathogen. Recombinant duplication of these proteins has resulted in four injectable medications approved for MS:

- Interferon beta-1a (Rebif[®], Avonex[®]); and
- Interferon beta-1b (Betaseron[®], Extavia[®]).

Interferons have a broad range of effects in the body, and while the exact mechanisms of their benefit on MS are unknown, the four beta interferon preparations are thought to work via similar mechanisms to suppress the activation of immune cells and limit their passage across the BBB (**Table 3**).⁸⁻¹⁰

Glatiramer Acetate

Glatiramer acetate (Copaxone[®]) is an antigen-based therapy for MS. (To recap: an antigen is a substance that triggers an immune response in the body. T and B cells have receptors for certain antigens on their surfaces.) Glatiramer acetate is thought to reduce damage within the CNS by suppressing inflammation and possibly contributing to the restoration of normal immune regulation. In animal models, glatiramer acetate has been associated with the release of neurotrophic factors that may limit damage to axons, but it is not known if this occurs in patients with MS (**Table 3**).¹¹

Ongoing trials of the platform therapies have elucidated more details about their specific mechanisms. Recent comparative trials of the interferons and glatiramer acetate have also shown comparable efficacy between the two classes.^{8,12-15} No new adverse effects related to long-term immunomodulation have emerged with the use of interferons or glatiramer acetate over periods extending 15 years or longer.¹⁶⁻¹⁸

Oral Agents for MS

Oral administration of DMTs has long been awaited in

Table 3. Platform Therapies in MS

Drug name	Taken as:	Thought to work by:	Main adverse effect concerns:
Interferon beta-1a (Avonex®)	Intramuscular injection 1 time/week	Minimize activation of immune cells that attack myelin; reduce travel of immune cells across the BBB	Injection-site reactions with subcutaneous formulations (not intramuscular formulation); flu-like symptoms; liver and thyroid function and blood counts must be monitored
Interferon beta-1a (Rebif®)	Subcutaneous injection 3 times/week		
Interferon beta-1b (Betaseron®)	Subcutaneous injection every other day		
Interferon beta-1b (Extavia®)	Subcutaneous injection every other day		
Glatiramer acetate (Copaxone®)	Subcutaneous injection every day	Modifies T cells specific to myelin to prevent attack; enhances "helper" and regulatory T cells; crosses BBB to react with cells specific to myelin turnover and reduce inflammation	Skin and injection-site reactions; postinjection reactions

BBB=blood:brain barrier.

the MS community. The oral therapies being studied in relapsing–remitting MS (RRMS) work by different mechanisms, including by depleting or sequestering populations of T cells. All have been studied primarily as monotherapy, although some are also being tested in combination with interferon beta or glatiramer acetate (**Table 4**). Several of these therapies may be associated with greater safety risks than the current injected therapies, based on results of Phase II and Phase III studies.^{19–26}

Fingolimod

Fingolimod, an oral immunodulator/immunosuppressant taken once daily, acts by sequestering lymphocytes (mainly T cells) in the peripheral lymph nodes. Fingolimod decreases circulating lymphocytes by approximately 70%, an effect that reverses after the drug is discontinued.²⁷

Fingolimod, under the brand name Gilenya™, received FDA approval on September 22, 2010. In a clinical trial versus placebo, oral fingolimod reduced the annualized relapse rate by more than 50% and the cumulative number of active lesions by up to 80%.¹⁹ After 2 years, 79% of patients in the treatment group remained free of active lesions and 77% remained relapse free. After 3 years, 60% of RRMS patients remained relapse-free. The Phase III TRANSFORMS

trial compared oral fingolimod (0.5 mg/day) with interferon beta-1a (Avonex®) in RRMS and showed superior outcomes for the oral agent at 12 months, including a lower annualized relapse rate (0.16 vs. 0.33; $P=0.001$), fewer active lesions, and a greater percentage of patients remaining relapse-free (83% versus 69%; $P=0.0001$).²⁰

Because fingolimod suppresses the body's immune response, infections are an important concern. In the TRANSFORMS trial, serious adverse events included 12 malignancies (versus two for Avonex®), most of which occurred in the skin.²⁰ In the longer placebo-controlled FREEDOMS trial, there was no difference in malignancies between two treatment groups and the placebo group.²¹ Two fatal herpes infections occurred in TRANSFORMS patients taking 1.25 mg of fingolimod daily, one of which was a case of primary disseminated varicella-zoster.²⁰ Bradycardia (lowered heart rate) or atrioventricular block, mostly asymptomatic, occurred as a first-dose effect in both fingolimod groups, although predominantly in the 1.25-mg dose group. Other reported adverse effects included mild hypertension, airway obstructions, increased intraocular pressure, macular edema, nasopharyngitis, dyspnea, headache, diarrhea, nausea, and asymptomatic liver enzyme elevations, all of which were more frequent in the higher-dose fingolimod arm.^{20,21}

Because of potential first-dose cardiopulmonary effects, the Gilenya™ labeling calls for medical observation for 6 hours after the first dose to monitor for signs and symptoms of bradycardia.²⁸ According to the labeling, the heart-rate decrease begins within an hour of the first dose, with the maximal decline at approximately 6 hours (the mean reduction in heart rate is 13 beats/minute).²⁸

Cladribine

Cladribine is a synthetic cytotoxic immunosuppressant that depletes T lymphocytes by causing apoptosis (cell death). Lymphocytes are particularly sensitive to an intracellular metabolite of this drug because they lack the enzyme necessary to further metabolize it. Intravenous (IV) cladribine is currently approved for treating hairy cell leukemia, under the brand name Leustatin®. Early studies of IV cladribine in MS showed a dramatic 90% reduction in gadolinium-enhancing lesions.²²

Oral cladribine's FDA application was denied in November 2009 and refiled in 2010, with a decision expected by the end of 2010. In the Phase III CLARITY trial comparing oral cladribine with placebo in 1,326 early RRMS subjects, those receiving cladribine had a 55% reduced risk of relapse and 30% lower pro-

gression of disability.²³

Long-term safety remains an important question with cladribine. Prolonged lymphopenia, the intended effect of the agent, is also the principal cause of toxicity. Higher doses of cladribine used in treating patients with cancer have been associated with life-threatening infections resulting from immunosuppression.²⁹ In the studies of IV and subcutaneous (SC) cladribine in MS, the most common adverse events were lymphocytopenia, infections (upper respiratory tract, urinary tract, herpes zoster), muscle weakness, purpura, injection-site reactions, hypertonia, and back pain. With oral cladribine, the most common treatment-emergent adverse event was the expected lymphopenia. A potential risk may be malignancies, which were observed in the CLARITY trial among four users of cladribine.²³ The effect of repeated dosing beyond 2 years in patients with MS is still being evaluated. Because this cytotoxic agent interferes with DNA and RNA processing, possible reproductive implications must also be considered. A single 1-week cycle of cladribine depletes some T-cell classes for more than a year and may affect several other immune cell types for 4 to 12 months, an indication of its long duration of action.²³

Table 4. Oral Disease-Modifying Therapies for MS

Drug name	Taken as:	Thought to work by:	Main safety concerns:
Cladribine	Oral, 2 to 4 cycles per year (Application submitted for FDA approval)	Depleting lymphocytes by causing cell death	Infections; reproductive risks; malignancies(?)
Fingolimod (Gilenya™)	Oral, daily (Approved)	Sequestering lymphocytes in the lymph nodes	Reduction in blood pressure and heart rate with first dose; possible cardiac conduction block; macular edema; shortness of breath; infections; liver damage
Fumarate (BG00012)	Oral, daily (Phase III studies in progress; also being tested as adjunct to platform agents)	Suppressing a cellular metabolic path important in inflammation and neuron preservation	GI side effects (diarrhea, vomiting); headache; fatigue
Laquinimod	Oral, daily (Phase III studies in progress)	Promoting anti-inflammatory cell development	Increases in liver enzymes; thrombosis
Teriflunomide	Oral, daily (Phase III study completed; also being tested as adjunct to platform agents)	Decreasing T and B cells	Reproductive risks; liver damage; GI side effects (nausea, diarrhea); paresthesia; pain

FDA=Food and Drug Administration; GI=gastrointestinal.

Laquinimod

Laquinimod is an oral daily drug currently under investigation in Phase III trials (including the BRAVO trial comparing laquinimod to Avonex®).³⁰ Laquinimod, considered by some MS experts to be an immunomodulator, is thought to exert anti-inflammatory effects by modulating cytokine balance in favor of Th2/Th3 cytokines. (Cytokines are proteins secreted by the immune cells when they are activated.)²⁴

In September 2010, the journal *Multiple Sclerosis* reported the results of a 36-week extension study of a Phase II trial of laquinimod in which patients originally randomized to placebo were switched to active drug.²⁵ Patients switching from placebo to laquinimod had a 52% decrease in the mean number of active lesions ($P=0.0006$).

Safety issues with laquinimod appear to be significantly lower than with fingolimod or cladribine. The main adverse effect of concern has been self-limited, dose-dependent increases in liver enzymes. A case of Budd-Chiari syndrome (venous thrombosis) occurred in one patient taking 0.6 mg of laquinimod in the Phase II trial.²⁵ One of the questions about this agent is whether its clinical efficacy will be sufficient for use as a monotherapy.⁸

Dimethyl Fumarate (also called 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.³¹ In MS, it acts as an immunomodulator, partly by suppressing oxidative stress-induced neuronal death. Fumarate is administered daily on a BID or TID schedule.

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%, reduced the relapse rate by 58%, and reduced new or enlarging T2 lesions.³²

Dimethyl fumarate has been relatively well tolerated in clinical trials. Predominant side effects have included gastrointestinal (GI) symptoms, headache, and fatigue.³²

Phase III trials of fumarate in MS are in process with results expected in 2011.³³ 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. The drug is also being studied in combination with interferon beta-1a.³³⁻³⁵

Teriflunomide

Another daily oral immunomodulator, 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.³⁶ 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.³⁷

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.³¹ Other safety issues include liver damage, GI adverse effects, paresthesia, and pain.³¹

A 2-year Phase III study has been completed and preliminary results were presented at the European Committee for Treatment and Research in Multiple Sclerosis' (ECTRIMS) meeting in October 2010.³⁸ The TEMSO study followed 1,088 patients with mild disability and an EDSS score of ≤ 5 . Patients received teriflunomide at a dosage of 7 mg or 14 mg or a placebo once a day. The annualized relapse rate for both doses of the drug was 0.37 at the end of the 108-week trial versus 0.54 for placebo. This equates to a relative risk reduction of 31%. Disability progression was also slowed and there was a reduction in total lesion volume with both doses. Adverse effects were similar for the active treatment and placebo groups, and there were no deaths.³⁸ Other Phase III studies, such as TOWER and TOPIC, are ongoing.^{39,40}

A Phase III combination study is in progress with teriflunomide added to interferon beta (TENERE).⁴¹ It is evaluating tolerability and safety, the number of gadolinium-enhancing lesions, and the burden of disease on MRI. Previously, teriflunomide was studied as an add-therapy to glatiramer acetate and interferon beta in a Phase II study, and found to be safe, with some evidence of additional effect on clinical signs of disease and MRI lesion burden.^{42,43}

It is likely that teriflunimode will be the next oral MS agent submitted to the FDA for marketing approval.

Monoclonal Antibodies for MS

Antibodies (or immunoglobulins) are blood-borne proteins produced by B-cells and plasma cells. In the body, their role is to identify and neutralize bacteria or viruses by binding to and recognizing the antigen in the infected cell. Monoclonal antibodies are bio-engineered substances designed to recognize specific antigens. In MS, monoclonal antibodies reduce or eliminate selected lymphocytes (T cells and/or B cells) in an effort to reduce their attack on myelin.⁴⁴ The long-term effects of depleting these types of immune cells in individuals with MS are unknown.

Therapy with certain monoclonal antibodies may require patients with MS to accept a tradeoff relative to the current platform therapies: potentially greater efficacy and a less-frequent dosing schedule in exchange for a higher risk of more serious side effects. The mechanisms and main safety concerns of natalizumab and some of the investigational monoclonal antibodies are shown in **Table 5**.⁴⁵⁻⁴⁸

Natalizumab

Natalizumab is indicated for the treatment of relapsing forms of MS and is primarily recommended for patients

who have had an inadequate response to or are unable to tolerate another MS therapy. This agent works by inhibiting the movement of T or B cells to the CNS by blocking alpha 4 integrins—proteins on the surface of the immune cell that allow it to cross the BBB. In key clinical trials (AFFIRM and SENTINEL), natalizumab reduced the risk of disability progression by 42% and the relapse rate by 68% compared to placebo, and by 24% and 54%, respectively, in patients taking interferon beta in combination with natalizumab compared to interferon beta plus placebo.^{45,46}

Natalizumab therapy has risks related to immunosuppression, most notably progressive multifocal leukoencephalopathy (PML), a rare and potentially fatal viral infection of the brain. As of October 2010, 72 cases of PML have occurred among 71,400 patients worldwide who have received natalizumab in the postmarketing setting, according to the manufacturer.⁴⁹ Most cases have occurred in patients receiving between 18 and 36 infusions, and higher rates have been observed in Europe than in the United States. The estimated risk of PML in people receiving 24-plus infusions is currently 1 in 1,000 cases. However, the longer-term risk of PML in people with MS receiving more than 30 infusions of natalizumab remains to be established.⁴⁹

Other monoclonal antibodies are being studied, and several are approved for other conditions such as rheu-

Table 5. Monoclonal Antibodies for MS

	How administered	Mechanism	Risks
Alemtuzumab (Campath®)	IV infusions (optimal cycle in MS to be determined)	Targets a surface antigen on many immune cells to neutralize their effect	Autoimmune reactions, including thyroid disease and platelet reduction with potential for bleeding; infections; infusion reactions
Daclizumab (Zenepax®)	IV infusion every 4 weeks; also can be administered SC	Binds to IL-2 receptor, an immune-signaling protein, limiting T-cell expansion; increases NK cells	Rash; infections
Natalizumab (Tysabri®)	IV infusion every 4 weeks	Prevents migration of immune cells across the BBB	Increased infection risk, including PML (a potentially fatal viral infection of the brain)
Ocrelizumab (humanized rituximab; Rituxan®)	IV infusions (optimal cycle in MS to be determined)	Binds to a surface antigen on B cells causing apoptosis and cytotoxicity	Systemic inflammatory response syndrome; profile still evolving

BBB=blood:brain barrier; IV=intravenous; MS=multiple sclerosis; NK=natural killer; PML=progressive multifocal leukoencephalopathy; SC=subcutaneous.

matoid arthritis (rituximab), leukemias (alemtuzumab), immune suppression following transplantation (daclizumab), or other malignancies (rituximab). Alemtuzumab is associated with the most profound degree of immunosuppression.^{8,44}

Selecting a Therapy: More Choices, Harder Decisions

Overall, the MS community will greatly benefit from the variety of treatment options available now and in the near future, but deciding which treatment is right for each patient becomes an even greater challenge.

One of the drawbacks of existing and newer therapies for MS is the lack of any reliable markers for determining which agent will work best for a given person. Other than the known breakdown of the disease by progressive and relapsing forms, investigators can't predict what makes MS more active in some people than in others, or which patients might respond best to glatiramer acetate, an interferon, or an immunosuppressive agent. Likewise, predicting which patients will experience adverse effects such as PML, another serious infection, or a malignancy is not yet possible. In the future, genomic research findings may be able to classify MS according to certain phenotypes that will help target therapies more closely to the biological activity.^{50,51}

One of the drawbacks of existing and newer therapies for MS is the lack of any reliable markers for determining which agent will work best for a given person.

For now, the clinicians treating MS must partner effectively with patients to make these decisions on an individual basis. Some areas for consideration include:

- **Adherence to therapies.** The availability of oral medications for MS will likely bring many patients to therapy who have been previously untreated due to their inability or unwillingness to use an injectable therapy. By some estimates, as many as half of patients with MS in the United States do not currently receive a DMT.⁵² While oral administration may have adherence advantages over injectables, it should be noted that adherence can be a problem with any type of medication, especially in chronic

illness. Side effects can significantly impact adherence. MS nurses treating patients who begin oral therapy should maintain open communication with patients about adherence issues.

- **Access to care and adherence to monitoring.** Monitoring is an essential step to limiting adverse effects and maximizing safety of any immunomodulating or immunosuppressive agent. In the case of fingolimod, recommended monitoring includes a required 6-hour observation period after the first dose to observe potential cardiac complications.²⁸ Blood tests are recommended to monitor leukocyte counts and liver enzymes, and fingolimod-treated patients should be made aware of any early signs of infection or liver problems.²⁸ Macular edema, a risk usually arising in the third to fourth month of fingolimod therapy, could be confused with an attack of optic neuritis. Thus, ophthalmologic monitoring is also recommended for those receiving fingolimod.²⁸

Regular blood tests are recommended for patients receiving interferons for MS as well, yet studies show adherence to this monitoring has been low.⁵³ Nurses must assess the degree to which patients using daily oral therapy will be able to adhere to the monitoring requirements.

- **Tolerability and acceptance of risk.** A patient's individual attitude toward risk often plays a key role in whether he or she will enter a clinical trial or a try a new, relatively unknown medical treatment. Some will accept any risk for a chance at a potentially greater reward; others are not willing to expose themselves to additional health risks or potential organ damage. Many are waiting to see whether any unforeseen complications (or changes in disease control) will occur among patients using new or experimental agents. In conversations with patients, it is important for the nurse to assess these attitudes, keeping in mind that risk acceptance often evolves as a person ages, decides to start a family, or experiences changes in disease or disability status.
- **Response to therapy.** How well an agent is controlling the disease is an overriding factor in any therapeutic decision. Determining how well a new therapy may be working may take several months or even years—in some cases it may not be clear whether a relapse is due to therapeutic failure or

might have happened regardless of therapy. Newer therapeutic categories may be more effective at controlling disease in some patients than in others.

Optimal control balanced with optimal safety is the ideal scenario. In some cases, this may involve combining more than one agent with favorable safety profiles to boost their efficacy. Trials are underway involving the oral agents fumarate, laquinimod, and teriflunomide alone and in combination with injectable therapies glatiramer acetate and interferon beta to determine whether an increased safety/efficacy balance is achieved.⁸

There may be “windows of opportunity” in the MS disease course when some drug categories are most effective.

- **Timing of treatment.** There may be “windows of opportunity” in the MS disease course when some drug categories are most effective. It is clear from recent clinically isolated syndrome (CIS) studies that the earliest stage of disease is an optimal time for many therapies that have mainly anti-inflammatory effects.^{54,55} However, clinical studies are also looking beyond CIS, at patients with active disease despite their use of a platform therapy. For example, in studies of natalizumab treatment for patients who continued to have active disease while receiving interferon treatment, the monoclonal antibody reduced disability progression by 24% and relapse rates by 54%.⁴⁶ Other trials have shown that glatiramer acetate is effective in cases of suboptimal response to beta interferons.^{56,57}
- **Patient preference, lifestyle, support, and cost reimbursement issues.** In the “real world,” the practical aspects of a therapy sometimes outweigh the efficacy aspects. A medication that sits in a cupboard instead of being used obviously is not helping the patient. Likewise for a medication that the patient can’t administer properly, is afraid to use because of fear of worsening side effects, or a prescription that the patient does not fill because of cost considerations. When long-term safety concerns for MS drugs were relatively equal, the “best” therapy for a patient often came down to the one that the patient

would use. Today, safety concerns must be balanced against efficacy, adherence, and cost considerations. There may be multiple acceptable options for a particular patient, and the best option may differ for one patient compared to another based on both individual factors of tolerability and risk, and the mechanism of action providing efficacy in disease suppression.

Conclusion

Educating patients about the pros and cons of available MS therapies requires time, knowledge, appropriate teaching tools, and follow-up. Neurologists and MS nurses will need to help patients establish reasonable expectations about their MS medications, methods of administration, mechanisms for ongoing monitoring, and potential side effects. Patients with MS need to understand that no new pill or therapy will erase MS, but that increased options represent more hope for better disease management and quality of life than ever before.

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Modifying the Immune System in MS: What We Know, What We're Learning

- Immunosuppressants for multiple sclerosis (MS) work primarily by depleting or suppressing the function or movement of large populations of lymphocytes (T and B cells). These agents have the tendency to lower the body's immune response to infection by opportunistic organisms.
- Immunomodulators, which include the current "platform therapies," interfere with portions of the immune process and leave other parts intact to fight off infections. Many MS therapies interfere with various steps in inflammation and immune attack on myelin by modifying the behavior of the immune cells.
- Oral administration of disease-modifying therapy has long been awaited in the MS community. The oral therapies being studied in MS work mainly by depleting or sequestering populations of T cells.
- Fingolimod acts by sequestering lymphocytes (T and B cells) in the peripheral lymph nodes. Fingolimod decreases circulating lymphocytes by approximately 70%, an effect that reverses after the drug is discontinued.
- Monoclonal antibodies reduce or eliminate selected lymphocytes (T cells and/or B cells) in an effort to limit their attack on myelin. The long-term effects of depleting these types of immune cells in individuals with MS are unknown.
- One of the drawbacks of existing and newer therapies for MS is the lack of any reliable markers for determining which agent will work best for a given person. Likewise, predicting which patients will experience adverse effects such as progressive multifocal leukoencephalopathy (PML), another serious infection, or a malignancy is not yet possible.
- For now, the clinicians treating MS have to partner with patients to make decisions about the optimal treatment regimen on an individual basis.
- When choosing a therapy, important areas for patient discussion and consideration include: adherence to therapies, access to care and adherence to monitoring, tolerability and acceptance of risk, response to therapy, timing of treatment, and patient-specific factors such as preference, adherence, lifestyle, support, and cost reimbursement issues.

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Modifying the Immune System in MS: What We Know, What We're Learning

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PLEASE SELECT THE BEST ANSWER

- In the context of multiple sclerosis, immunomodulation and immunosuppression are basically the same thing.**
 - True
 - False
- Which of the following are lymphocytes?**
 - Macrophages
 - Neutrophils
 - T and B cells
 - All of the above
- Which of the following best describes the immune system in the pathology of MS?**
 - Myelin releases antigens that attract proinflammatory cytokines
 - The immune system reacts to "self" antigens by sending lymphocytes to attack myelin
 - Macrophages consume cells that would normally protect myelin in the central nervous system (CNS)
 - All of the above
- Which of the following describes the role of B cells in MS?**
 - They have a lesser role than T cells in causing CNS damage
 - They have a greater role than T cells in causing CNS damage
 - They potentiate the role of T cells in causing CNS damage
 - None of the above
- Adverse effects of immunosuppression in MS include all BUT which of the following?**
 - Infection
 - Malignancies
 - Autoimmune diseases
 - Acquired immunodeficiency syndrome
- Which of the following is true of beta interferon and glatiramer acetate therapies for MS?**
 - Efficacy is significantly lower than that seen in placebo-controlled trials of newer oral agents
 - No head-to-head trials are available comparing these agents with each other in MS
 - Significant immunosuppression-related risks have been observed with their use
 - No significant adverse effects relating to immunomodulation have been observed
- Fumarate, laquinimod, and teriflunomide are examples of:**
 - approved oral disease-modifying therapies (DMTs) for MS
 - oral agents approved in other diseases and used off-label for MS
 - investigational oral agents for MS
 - injectable therapies for MS
- Oral agents for MS are generally regarded as safer than injectable medications because of the simpler mode of administration.**
 - True
 - False
- The primary safety concern with the use of the monoclonal antibody natalizumab in patients with MS is:**
 - progressive multifocal leukoencephalopathy (PML)
 - postinfusion reactions
 - lack of efficacy
 - none of the above
- Recommended monitoring for patients with MS receiving fingolimod includes all of the following EXCEPT:**
 - observe for bradycardia for 6 hours after the first dose
 - order routine Holter monitoring after 3 months
 - monitor leukocytes and liver enzymes
 - monitor for macular edema

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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. Discuss immunomodulation in the context of the current first-line medications available for multiple sclerosis (MS)..... 5 4 3 2 1
- 2. Describe categories of investigational drugs for MS and how their mechanisms may contribute to immunosuppression 5 4 3 2 1
- 3. Evaluate risks associated with immunosuppression in MS..... 5 4 3 2 1
- 4. Identify issues for discussion with patients with MS in the selection of appropriate disease-modifying therapies..... 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
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