Multiple Sclerosis: Emerging Oral Therapy

Dr. Thomas A. Gossel and Dr. J. Richard Wuest have no relevant financial relationships to disclose.

Goal. The goal of this lesson is to describe emerging oral therapy for treatment of multiple sclerosis.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. identify factors known to reduce adherence with parenterally administered drugs in multiple sclerosis, and the factors that enhance adherence;
2. recognize the pharmacologic classification of the emerging oral therapy discussed in this lesson;
3. demonstrate an understanding of the mechanism of action, major adverse events and therapeutic applications associated with the drugs; and
4. exhibit knowledge of information relative to multiple sclerosis pharmacotherapy to convey to patients.

Multiple sclerosis (MS) is a chronic, potentially debilitating immune-mediated disease of the central nervous system (CNS) that affects about 400,000 people in the United States, with another 200-plus new cases diagnosed each week. It is not an homogeneous disease entity and, therefore, as new pharmacotherapies emerge, it will require individual therapy regimens. As a chronic and so far incurable disease, therapy is required for an indefinite, perhaps lifelong, period of time.

The current concept of MS treatment entails use of drugs that influence immunological reactions. These therapies alter the course of this pathology and reduce the grade of disability. There are no definite symptoms to predict the individual course of disease in its early stages, and the individual grade of disability in the future cannot be anticipated with certainty. Consequently, ideal treatment of MS would fulfill the general criteria of: maximal efficacy (ideal: cure), minimal adverse effects (ideal: none), maximal patient adherence (ideal: 100 percent), and easy dosing regimens.

Current disease modifying therapy (DMT) [Table 1] for the chronic treatment of relapsing-remitting multiple sclerosis (RRMS), such as interferon-beta (IFNβ)-1b (Betaseron, Extavia), IFNβ-1a (Avonex, Rebif), glatiramer (Copaxone), mitoxantrone (Novantrone, and others) and natalizumab (Tysabri) has benefitted the course of MS favorably. IFNβ or glatiramer acetate have become the gold standard of care (first-line) for modifying the course of RRMS, with mitoxantrone or natalizumab used when the first-line agents fail to provide suitable relief or when adverse events prevail. In randomized controlled Phase III trials, all of these parenterally-administered agents demonstrate superiority to placebo regarding clinical endpoints. Recently published comparative trials failed to provide evidence for superiority of one or the other first-line DMTs. Still, there are opportunities for additional improvements by further reducing relapse rates, slowing disease progression and providing more convenient treatments that do not rely on administration by injection. The first orally-administered DMT, fingolimod (Gilenya), was approved in September 2010 for treating RRMS.

Clinical Benefit with Disease-Modifying Therapy

DMTs offer some degree of benefit to most patients with MS. At the same time, certain patients respond only to specific DMTs, which suggests there may be genetically-based differences in drug response (pharmacogenomics) and perhaps also, based on recent pathologic studies in MS, immunopathologic disease subtypes that may require different therapeutic approaches. Approval of new drugs that have different physicochemical proper-
ties and different mechanisms of action compared to currently available DMTs may offer a means to achieve treatment goals in a broader spectrum of patients.

**Shortcomings of Parenteral DMT**

With the exception of fingolimod, currently approved DMTs must be delivered parenterally. Parenteral administration necessitates frequent injections, which may be uncomfortable and/or inconvenient for patients. Although self-administration is an option with the interferons and glatiramer, giving the patient greater freedom, this can also be a constant reminder of their chronic disease. Regular hospital or clinic visits are needed for intravenous infusions of natalizumab or mitoxantrone for relapsing forms of MS that continue to worsen.

One in five persons in the general population suffers from injection anxiety (needle phobia). This anxiety may prevent those with MS from self-injecting their drugs. Other factors (Table 2), such as misunderstanding concerning risks of self-injection or a lack of knowledge about how best to manage injection pain and side effects, can contribute to inability to self-administer injections. Many patients view injections as a bothersome burden, rather than a means to manage their disease.

Patient acceptance of treatment may be negatively affected by injection-site reactions. These local reactions such as edema, redness and pain may be initiated by subcutaneous administration and to less extent, with intramuscular injection. They are a common reason for switching from subcutaneous IFNβ to intramuscular therapy. Usually mild, injection-site reactions are reported to occur in up to 80 percent of patients using subcutaneous IFNβ. Patient discomfort during and after injections contributes to treatment dissatisfaction and is a known factor affecting adherence. Eight to 12 percent of patients who switch or stop IFNβ injections do so because of injection-site reactions. Although uncommon, injection-site necrosis has also been reported.

**The Importance of Adherence.** Poor adherence with DMT regimens correlates with poor clinical benefit. Improving efficacy of drugs used to treat MS requires close adherence to DMT protocols. Poor adherence to treatment regimens is associated with increased patient morbidity, poorer quality of life and increased financial burden on healthcare programs and institutions.

MS is a chronic disease that requires treatment lasting over many years, often a lifetime. This places a burden on patients to adhere closely to their therapy indefinitely. Repetitive studies have confirmed significant dropouts from therapy within the first two years, and sometimes within the first six months of treatment. A long-term, follow-up study over 4.2 years found that discontinuation rates were as high as 46 percent. Twenty-eight percent of these patients suspended therapy because of a perceived lack of efficacy.

Studies in patients with MS support the contention that the same principles underlying adherence to treatment in other chronic disease states such as hypertension and diabetes mellitus also apply to MS. Potential barriers to therapeutic adherence with DMTs include denial of illness especially early in its course, interference in lifestyle by treatment requirements, adverse effects of treatment, cost of therapy, injection anxiety, difficulties with self-injection techniques, cognitive impairment, unrealistic expectations for the drugs, depression and lack of confidence in drug efficacy. For example, a breakthrough relapse in MS following a long period without visible symptoms may convince the patient that the therapy is ineffective, which can lead to a perception that the costly medicine is not effective, and lead to missed doses or other actions that amount to poor adherence.

It has also been reported that many patients have unrealistic expectations of efficacy, which can lead to poor adherence. An interview with 99 MS patients who were started on IFNβ-1b therapy revealed that 57 percent had unrealistic, overly optimistic expectations regarding reduction in relapse rate. Education on the expected outcomes of therapy lowered that percentage to 33 percent. Among patients who discontinued therapy, 64 percent had overly optimistic expectations. In contrast, only 28 percent of the patients who were compliant with therapy expressed overly optimistic expectations.

### Table 1
Approved disease-modifying therapy for treatment of multiple sclerosis

<table>
<thead>
<tr>
<th>First-line</th>
<th>Trade names</th>
<th>Dosage form</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferonβ-1b</td>
<td>Betaseron</td>
<td>SC injection</td>
<td>0.25 mg every other day</td>
</tr>
<tr>
<td>Interferonβ-1b</td>
<td>Extavia</td>
<td>SC injection</td>
<td>0.25 mg every other day</td>
</tr>
<tr>
<td>Interferonβ-1a</td>
<td>Avonex</td>
<td>IM injection</td>
<td>30 µg once weekly</td>
</tr>
<tr>
<td>Interferonβ-1a</td>
<td>Rebif</td>
<td>SC injection</td>
<td>22-44 µg 3 times weekly</td>
</tr>
<tr>
<td>Glatiramer</td>
<td>Copaxone</td>
<td>SC injection</td>
<td>20 mg daily</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Gilenya</td>
<td>Oral capsule</td>
<td>0.5 mg once daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second-line</th>
<th>Trade names</th>
<th>Dosage form</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone</td>
<td>Novantrone, &amp; others</td>
<td>IV injection</td>
<td>12 mg/m² given as a short (5-15 min) infusion every 3 months</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Tysabri</td>
<td>IV injection</td>
<td>300 mg infused over 1 hour every 4 weeks</td>
</tr>
</tbody>
</table>

SC, subcutaneous; IM, intramuscular; IV, intravenous

Table 2
Non-adherence to treatment: contributory factors, strategies adopted in MS therapy to address adherence, and currently unmet needs for improvement

<table>
<thead>
<tr>
<th>Factors that have a negative effect on adherence to treatment for chronic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Time taken to administer</td>
</tr>
<tr>
<td>• Complexity of treatment regimen</td>
</tr>
<tr>
<td>• Difficulty with administration of treatment</td>
</tr>
<tr>
<td>• Adverse effects of treatment</td>
</tr>
<tr>
<td>• Disruption of lifestyle by therapy</td>
</tr>
<tr>
<td>• High frequency of dosing</td>
</tr>
<tr>
<td>• Cost of medication</td>
</tr>
<tr>
<td>• Injection phobia</td>
</tr>
<tr>
<td>• Unrealistic therapeutic expectations</td>
</tr>
<tr>
<td>• Depression</td>
</tr>
<tr>
<td>• Treatment fatigue</td>
</tr>
</tbody>
</table>

**Approaches that have been applied to improve treatment adherence in MS**

- Co-medication with oral drugs (e.g., acetaminophen, ibuprofen) that reduce flu-like symptoms associated with DMTs
- Auto-injection devices to make self-injection easier
- New formulations of DMTs that do not require refrigeration and reconstitution
- Treatment of depression
- Implementing educational interventions to improve understanding of rationale, expectations and potential adverse effects, including nurse training programs to optimize injection techniques at treatment initiation
- Reinforcement of adherence on a regular basis to encourage use as directed

**Unmet needs for improving treatment adherence in MS**

- Availability of non-injected therapy
- Simple treatment regimens
- Less expensive therapy
- Improved benefit-to-risk ratio

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Unmet needs were decreased with the September 2010 approval of fingolimod (Gilenya).

MS, Multiple sclerosis; DMT, disease-modifying therapy


**Achieving Optimal Adherence.** Helping patients achieve optimal adherence to their medical treatment protocol is an area where pharmacists can play a significant role. It has been shown that patients who have positive feelings toward prescribed therapy adhere more closely to their regimen than those who have more negative feelings. Adherence, therefore, reflects an active decision process on the part of patients, and this can be influenced positively with pharmacist counseling. Advising against skipping doses or discontinuing therapy is certainly within the realm of counseling information to convey to patients. To counter non-adherence, the patient must understand the purpose of the therapy and have reasonable expectations for its benefit, understand the potential adverse effects and perceive value in taking the therapy correctly to control or prevent disease manifestations that outweigh inconvenience or negative effects.

It is anticipated that the development of drugs with easier means for administration, such as oral agents, would further promote strong patient adherence. There are examples of disease requiring long-term therapy where a move towards non-injected agents has been a valuable and important addition to the treatment regimen. The availability of effective oral DMTs does not eradicate non-adherence, but represents improved likelihood for a significant advance in treatment of patients with relapsing forms of MS compared with parenterally-administered drugs.

**The Floodgate for Oral Therapies Has Opened**

**Fingolimod.** Approval of a first-line oral formulation (Gilenya) for treating relapsing forms of MS is welcome news for patients. Formerly known as FTY720, the drug is a synthetic structural analog of sphingosine 1-phosphate (S1P), which is an endogenous lysophospholipid, a potent signaling lipid that targets sphingosine 1-phosphate receptors. S1P interacts with five known subtypes of S1P receptors (S1P₁-₅) distributed throughout the body. S1P₁ and S1P₂ are found throughout the immune, cardiovascular and central nervous systems. Their activation on smooth muscle and endothelial cells regulates vascular homeostasis and permeability. Activation of S1P₁ receptors on atrial muscle regulates heart rate. S1P₃ response is generally confined to the hematopoietic and lymphoid tissues, and S1P₅ is expressed in the white matter of the CNS.

Fingolimod undergoes rapid phosphorylation *in vivo* within the CNS by sphingosine kinase into fingolimod-phosphate, the biologically active compound. Fingolimod-phosphate is a nonselective S1P agonist that binds with four of the five S1P receptor subtypes (S1P₁, S1P₂, S1P₃, S1P₄, and S1P₅) to modify their signaling pathways. The drug readily crosses the blood-brain-barrier to interact with S1P receptors that are widely expressed throughout the CNS. Binding to S1P₁ receptors that are highly expressed on T and B lymphocytes is responsible for regulating their egress from lymphoid tissue. This egress is essential for normal immune function. Binding to S1P₁, down-regulates the receptor with subsequent sequestration (isolation) of lymphocytes in the lymph tissue, to prevent their recirculation, and reduce peripheral lymphocyte counts. Fingolimod is not believed to destroy lymphocytes; therefore, many immune functions including activation, proliferation and effector functions of T and B lymphocytes remain undisturbed during treatment. However, immune function that relies on naïve T cells and central memory cells, such as activity that is necessary to combat viral infections, may be reduced or delayed. Given the theory that aggressive lymphocyte penetration into the CNS contributes to inflammation and neural degeneration via demyelination found in MS, the drug’s major benefit may be due to its ability to sequester lymphocytes within the lymphoid...
tissues. Moreover, S1P, receptors expressed in the CNS are known to modulate neurogenesis (production of neurons) and neural function. Fingolimod may, therefore, be able to facilitate restoration of nerve cell function and supplement endogenous CNS repair.

The most common adverse events reported in 10 to 20 percent of fingolimod-treated patients in pre-marketing trials included fatigue, melanocytic nevus, (moles), influenza virus infection, lower respiratory tract or lung infection, back pain, diarrhea, cough, and abnormal liver function tests. Effects occurring in more than 20 percent of fingolimod-treated patients were nasopharyngitis and headache. Serious adverse events occurred in 7 to 11 percent of patients and included MS relapse, basal cell carcinoma and transient sinus bradycardia.

Other clinical adverse events observed during these trials are notable. Macular edema was reported in a small percentage of patients. Six of seven cases resolved within six months upon drug discontinuation. Skin cancer was reported in Phase II testing. In two trials, 15 fingolimod-treated patients were found to have skin cancer, all successfully excised. Laboratory abnormalities included decreased lymphocyte count, mild decrease in mean forced expiratory volume in one second (FEV), and a reversible increase of alanine transferase to greater than three times the upper limit of normal.

The product’s manufacturer lists four drugs or drug classes that should be used cautiously, if at all, with fingolimod. These include class Ia (e.g., quinidine) or Class III (e.g., amiodarone) antiarrhythmics, beta-adrenergic blockers, ketoconazole and vaccines.

Emerging Options for Oral Therapy in MS
The new generation of MS therapies will continue to expand. Intensive research into the complex interplay of biochemical and physiological processes involved in the pathophysiologic cascade of the disease has identified a variety of potentially new targets for oral therapeutic strategies. Data showing efficacy for these new oral agents are impressive, and reveal they have the potential to eventually replace injectable DMT options. Any new treatment regimen, however, brings concerns relating to safety and cost. In addition as noted above, patients with MS have poor treatment adherence to the currently available parenteral therapies, and it remains uncertain whether the introduction of oral agents will improve patient adherence. Moreover, advancement into Phase III trials may not always result in a new therapy, as was recently shown when an oral version of glatiramer failed to improve the rate of relapses in a clinical trial involving 1651 patients with RRMS.

Cladribine. Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analogue prodrug. It is selectively toxic for lymphocytes and monocytes, appears to cross the blood-brain-barrier with ease, and has preferential lymphocyte-depleting properties. It is currently used in an intravenous formulation (Leustatin) as an effective approved therapy for hairy cell leukemia and other hematologic malignancies, in patients unresponsive to other therapy. It has also been assessed in clinical trials for treatment of a variety of autoimmune diseases. Administered orally, the drug has been shown to be effective in treatment of RRMS.

The mechanism by which cladribine acts in MS is not fully known; however, there is evidence that it is phosphorylated intracellularly by deoxycytidine kinase to 2-chlorodeoxyadenosine triphosphate, which accumulates within cells to disrupt cellular metabolism and inhibit DNA synthesis and repair, and subsequently induce apoptosis (natural or programmed cell death). This occurs preferentially in lymphocytes, thus depleting the level of activated lymphocytes that induce central neuron demyelination in MS. It also spares other hematologic and immune cells such as B cells and natural killer cells. The primary effect of cladribine is immune cell depletion, and the drug depletes both proliferating and inactive lymphocytes.

Results of Phase II and III trials in MS employing an injectable formulation of cladribine demonstrated suppression of gadolinium-enhancing lesions in patients with RRMS who received cladribine for six months compared with placebo. Cladribine also reduced the frequency and severity of relapses compared with placebo at the 12- and 18-month time points. The sustained immunosuppressive effects of cladribine would make it ideal for intermittent dosing, which should improve patient adherence and tolerability. Current trials are evaluating oral cladribine for use as monotherapy or in combination with IFNβ-1a to augment its efficacy.

A standard dosing regimen for oral cladribine has yet to be established and two possible dosing regimens are being explored in these studies. These doses have been associated with a good safety and tolerability profile. Myelosuppression is the dose-limiting toxicity, and culture-negative fever is the most common adverse effect. No events related to cardiotoxicity, nephrotoxicity or neurotoxicity have been reported. While lymphopenia that occurs following a single course of cladribine may be considered a risk factor for infection, opportunistic infection has occurred in only a few patients with cases limited to mild herpes zoster along with one fatal hepatitis B infection.

BG00012. This is an oral formulation of dimethylfumarate that has anti-inflammatory and neuroprotective properties, and is used for treatment of psoriasis in some European countries. The drug is being evaluated in two Phase III trials. Studies in psoriasis patients indicate that it decreases peripheral counts of CD4+ and CD8+ lymphocytes, particularly the latter.

Treatment with BG00012 led to
a statistically significant reduction in the total number of gadolinium-enhancing brain lesions, as measured by MRI over six months of treatment. The most commonly reported adverse events included flushing, gastrointestinal disorders, headache and nasopharyngitis. Liver enzyme elevations were reported in 2 to 5 percent of the treatment groups, compared with 5 percent in the placebo group.

Its exact mechanism of action is still unclear, but it appears the drug has a novel mechanism of action as potential therapy for MS. It possesses both cytoprotective and anti-inflammatory properties through inhibiting expression of pro-inflammatory cytokines and cell adhesion molecules. Studies have demonstrated that dimethyl fumarate treatment may suppress peripheral CD4+ and CD8+ lymphocytes and may also shift the predominant T lymphocyte population from a T helper (Th1) to a Th2 phenotype. This is also one of the presumed mechanisms of action of glatiramer.

**Firategrastr.** Like natalizumab, firategrastr is an alpha-4-integrin antagonist that interferes with the binding of α4β1 and α4β7 integrins to its ligand, VCAM-1. This prevents the migration of immune cells into the CNS. Clinical trials have shown a decrease in new lesions with a trend toward fewer relapses with increasing doses.

Firategrastr was generally well tolerated in clinical trials. Adverse events included vomiting; infections, particularly of the urinary and respiratory tract; and rash. At this time, there are no reports of progressive multifocal leukoencephalopathy (disease of the white substance of the brain).

Unlike natalizumab, it is a small molecule in the form of an oral preparation. This confers the benefit of a more convenient mode of delivery along with improved patient adherence to therapy.

**Laquinimod.** Laquinimod, a quinoline-3-carboxamide derivative, is chemically distinct from roquinimex (Linomide), an agent that has demonstrated efficacy in the oral treatment of MS but is associated with substantial adverse effects. Laquinimod is more potent at inhibiting MS symptoms than its parent compound and reportedly causes fewer adverse effects.

Although its pharmacologic target has not been definitely identified, laquinimod is believed to inhibit the infiltration of both CD4+ T cells and macrophages into the CNS. Its efficacy is also believed to be at least partially due to shifting the balance of the T lymphocyte population in favor of cells expressing Th2/Th3 cytokines, interleukin (IL)-4, IL-10 and transforming growth factor-beta. This novel action produces an immunomodulatory response (altered immune response) without causing immunosuppression. The T cell shift indicates the beneficial effects of laquinimod occur because of a deviation of the immune response, rather than suppression. Results of a recently published study that compared the effects of laquinimod in the peripheral blood mononuclear cells of healthy subjects and patients with RRMS showed that the drug induced suppression of genes associated with antigen presentation and the resulting inflammatory pathways.

Laquinimod has been shown to suppress active lesions on MRI scans in patients with RRMS. In a Phase II trial in patients with RRMS, laquinimod showed a favorable safety profile, without significant clinical or laboratory signs of undesired inflammatory manifestations such as serositis (inflammation of serous membranes) or myocardial infarction. In a 24-month open-label extension trial, laquinimod was well tolerated. The most frequently reported adverse events were nasopharyngitis (25.8 percent), back pain (12.4 percent), and headache (8.1 percent).

**Teriflunomide.** Teriflunomide is the active metabolite of leflunomide (Arava), an approved treatment for rheumatoid arthritis. Teriflunomide inhibits T cell activation through reversible inhibition of dihydroorotate dehydrogenase, the rate-limiting step in the de novo synthesis of pyrimidine, leading to decreased DNA synthesis. This novel action during the induction of cellular immune responses is thought to contribute to its clinical effectiveness in diseases characterized by exaggerated immune reactions. Further effects on inflammatory cell recruitment and other in vitro immunomodulatory processes are postulated. In a Phase II trial of 157 patients with RRMS and 22 with progressive MS, oral teriflunomide was shown to decrease the number of unique, active MRI lesions.

The treatment seems to be well tolerated and the frequency of adverse events was similar across groups. This drug has entered Phase III trials as monotherapy, and is also being investigated in combination with either IFNβ or glatiramer in Phase II trials.

**Dalfampridine.** Also known as fampridine, dalfampridine (Ampyra) is an old drug in new clothing. Its active ingredient is 4-aminopyridine (4-AP), a compound developed initially as a bird poison. For more than three decades, 4-AP has enjoyed off-label use in humans for treatment of MS. At the same time, it remained a niche drug because of limited effectiveness, limited availability only through specialized compounding pharmacies, and a substantial seizure risk. It is a selective potassium channel antagonist that is believed to relieve MS symptoms by restoring conduction in demyelinated axons via voltage-dependent potassium channel blockade. The drug was approved for treatment of patients with MS in January 2010, and is unique among MS pharmacotherapy in being indicated specifically for improving walking ability and lower leg strength (as opposed to reducing relapses or improving disability). The drug is not a DMT, and has not shown efficacy in any other domain apart from improved walking.

Dalfampridine is an extended-release formulation of 4-AP that
has favorable pharmacologic properties compared with its generic forebear, including twice-daily instead of three-times-daily dosing without regard to meals. In preliminary trials, seizures were still a problem at doses of 20 mg twice daily and above. Therefore, a dose of 10 mg twice daily was chosen for the phase III trials. Given the low safety factor for the drug, it is likely that seizures will ultimately emerge as an expected adverse effect with continued use.

To date, no formal drug interaction studies with dalfampridine have been conducted. Because it may lower the seizure threshold, precaution should be taken in patients who are concomitantly taking medications that may also induce seizures, such as tricyclic antidepressants, phenothiazines and venlafaxine. Ampyra is distributed exclusively through a network of specialty pharmacies, which are coordinated by Ampyra Patient Support Services.

**Side Note**
Several monoclonal antibodies are under study as possible treatments for RRMS. These therapies will not be orally administered; however, they do target different sites on immune cells and may offer alternatives for patients who have not responded adequately to current treatment options.

**Alemtuzumab (Campath).** Alemtuzumab is currently approved as a treatment for B cell chronic lymphocytic leukemia. The drug was given an FDA Fast Track designation in 2010 for study in RRMS, and Phase III trials are underway.

**Daclizumab (Zenapax).** This appears to increase numbers of CD56 natural killer cells and in a Phase II clinical trial reduced the number of new or enlarging gadolinium-enhancing lesions by 72 percent when combined with IFNβ-1b, compared to IFNβ-1b alone. The drug is currently approved for prophylaxis against acute rejection in renal transplant patients.

**Rituximab (Rituxan).** Approved for treatment of non-Hodgkin’s lymphoma, rheumatoid arthritis and chronic lymphocytic leukemia, rituximab, which targets and depletes CD20+ B lymphocytes, reduced lesion burden and relapse rate compared with placebo, and reduced relapses when used as an add-on to conventional injectable therapies in Phase II trials of patients with RRMS.

**Overview and Summary**
Newer treatment options for patients with MS have improved efficacy over first-generation therapies; however, they still necessitate the use of weekly or monthly injections. Emergence of a new generation of oral MS agents would, in theory, not only eliminate the need for painful injections and provide patients with a more user friendly alternative to currently approved choices, but these compounds also show promise in reducing the number and volume of brain lesions. Although the results of Phase II and III oral therapy trials are encouraging, all agents have significant adverse effects that may outweigh positive benefit in certain individuals. These oral therapies may, therefore, not displace the existing platform therapies, but be used along with them.

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This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

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1. All of the following are correct descriptions of multiple sclerosis (MS) EXCEPT:
   - a. chronic.  
   - b. debilitating.  
   - c. heterogeneous.  
   - d. immune-mediated.

2. Which of the following types of interferon (IFN) has become the gold standard of care for modifying the course of relapsing-remitting multiple sclerosis (RRMS)?
   - a. Alpha  
   - b. Beta  
   - c. Gamma  
   - d. Delta

3. The first orally administered disease-modifying therapy (DMT) for treating patients with MS is:
   - a. fingolimod.  
   - b. glatiramer.  
   - c. mitoxantrone.  
   - d. natalizumab.

4. The intramuscularly administered DMT product for treating patients with MS is:
   - a. Rebif.  
   - b. Extavia.  
   - c. Betaseron.  
   - d. Avonex.

5. It has been reported that more than half (57 percent) of patients with poor adherence for MS therapy have unrealistically optimistic expectations regarding the:
   - a. difficulty in self-administering the injections.  
   - b. feeling they will ever get better.  
   - c. high incidence of injection site reactions.  
   - d. reduction in relapse rate.

6. The type of sphingosine 1-phosphate receptor targeted by Gilenya that is located on atrial muscles that regulates heart rate is:
   - a. S1P\(_1\).  
   - b. S1P\(_2\).  
   - c. S1P\(_3\).  
   - d. S1P\(_4\).

7. By hindering S1P\(_1\), Gilenya causes all of the following EXCEPT:
   - a. prevention of recirculation of lymphocytes.  
   - b. increased peripheral lymphocyte count.  
   - c. sequestration of lymphocytes in the lymph tissue.  

8. The major benefit of Gilenya is thought to be its ability to cause:
   - a. prevention of recirculation of lymphocytes.  
   - b. increased peripheral lymphocyte count.  
   - c. sequestration of lymphocytes in the lymph tissue.

9. The manufacturer of Gilenya warns that all of the following drugs should be used cautiously, if at all, with Gilenya EXCEPT:
   - a. amiodarone.  
   - b. ketoconazole.  
   - c. mirtazapine.  
   - d. quinidine.

10. Cladribine is selectively toxic for lymphocytes and:
    - a. erythrocytes.  
    - b. granulocytes.  
    - c. leukocytes.  
    - d. monocytes.

11. By inhibiting DNA synthesis and repair, cladribine subsequently induces natural or programmed cell death, a process referred to as:
    - a. apoptosis.  
    - b. biodegradation.  
    - c. cytotoxicity.  
    - d. necrosis.

12. Firategrast:
    - a. decreases DNA synthesis by affecting the synthesis of pyrimidine.  
    - b. prevents migration of immune cells into the CNS.  
    - c. regenerates neuronal tissue into its functioning form.  
    - d. stimulates the production of myelin in central neurons.

13. Laquinimod produces an:
    - a. immunosuppressant response.  
    - b. immunomodulatory response.

14. Teriflunomide:
    - a. decreases DNA synthesis by affecting the synthesis of pyrimidine.  
    - b. prevents migration of immune cells into the CNS.  
    - c. regenerates neuronal tissue into its functioning form.  
    - d. stimulates the production of myelin in central neurons.

15. Dalfampridine was developed initially as a:
    - a. rat poison.  
    - b. insecticide.  
    - c. fungicide.  
    - d. bird poison.

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