MULTIPLE SCLEROSIS: ORAL DISEASE-MODIFYING AGENTS FOR RELAPSING FORMS OF MS

Multiple Sclerosis: Oral Disease-Modifying Agents For Relapsing Forms Of MS

Since 2009, three new oral agents for relapsing forms of multiple sclerosis (MS) have been approved:

- Fingolimod (Gilenya®)
- Teriflunomide (Aubagio®)
- Dimethyl fumarate (Tecfidera®)

All three medicines are approved for the treatment of relapsing forms of MS. All three reduce the rate of relapses of MS, reduce new or enhancing MRI lesion formation, and may slow progression of MS. None of these are related to the older injectable agents for MS, and all have their own mechanism of action (how they work in MS).

All are approved as first-line treatments for relapsing forms of MS, but long-term use has not been extensively studied in these medicines due to their recent release on the market. Many insurance plans require that one or two injectable agents be tried before using one of the oral agents. We usually consider a standard injectable agent as a first choice unless there are specific reasons to begin with one of these oral agents. All of these medicines have their own mechanism of action, side effect profile, and monitoring protocol.

Fingolimod (Gilenya)

Fingolimod (Gilenya) is a medicine which acts by blocking the exit of lymphocytes (immune cells that the body forms which may cause injury in the brain and spinal cord in MS) from the lymph nodes.

Gilenya is administered as a once a day pill (0.5 mg) in a standard dose. Higher doses were not shown to work better than this dose.

Fingolimod is generally safe and well tolerated but there are important safety issues that must be evaluated prior to and after starting the medicine.

- **Slowing of heart rate.** Heart rate consistently slows following administration of the 1st dose of Gilenya, and rarely more significant heart rhythm issues may occur. Typically these changes do not cause symptoms, reach a maximum 4 to 5 hours after the 1st dose, and subsequently, return to normal over 1 to 2 weeks. Very rarely, patients develop symptoms (lightheadedness, dizziness, palpitations, chest pain, etc.) or more worrisome abnormalities on the EKG and may require intervention. Patients with various heart rhythm problems, abnormal electrocardiograms, or with significant heart disease may not be candidates for this medicine. Monitoring patients in a physician's office for signs and symptoms of bradycardia or AV slowing for 6 hours after the 1st dose is required. If a patient stops Gilenya for 2 weeks, monitoring will be required again when it is restarted.
- **Macular edema.** Rarely, patients treated with. Gilenya develops macular edema (a swelling of the tissues in the back of the eye, causing blurred vision). It usually develops within 3 to 6 months after starting Gilenya and improves or resolves with discontinuation of Gilenya. Patients with diabetes and uveitis are at increased risk for macular edema from Gilenya. Patients should have an eye exam prior to starting Gilenya and 3 to 4 months after starting treatment. Patients should be instructed to notify their care team if they develop blurred vision after starting Gilenya.
- **Liver abnormalities.** Rarely, Gilenya causes elevation of liver tests, typically mild and reversible. Monitoring liver tests for these increases may be necessary after beginning fingolimod.
- **Increased blood pressure.** Blood pressure typically increases mildly during the first 6 months of treatment with Gilenya then stabilizes. Patients with known hypertension should have their BP monitored while on Gilenya and their antihypertensive regimen adjusted as needed.
- **Infections.** Gilenya is a potent immunomodulatory drug and reversibly lowers blood lymphocyte counts. Therefore, there is some concern about the risk of infections with Gilenya, though major infections were not a frequent complication of this medicine in the research trials. Gilenya should be used with caution in patients with recurrent or chronic infections. Gilenya may increase the risk of viral illnesses such as chicken pox and shingles. Patients who do not have immunity against this virus should undergo vaccination with a chicken pox vaccine.
- **Other side effects.** Occasionally, patients may develop cough or shortness of breath which requires evaluation. Other rare side effects include headache, diarrhea, back pain, and vascular disorders.

Teriflunomide (Aubagio)

Teriflunomide was approved in 2012 for relapsing forms of multiple sclerosis. There are two doses, a 7-mg and a 14-mg pill, both of which are given once a day orally. Teriflunomide reduced relapse rate and MRI lesion formation, and the higher dose reduced progression of disability.

The exact mechanism of teriflunomide is not known, but it may reduce the number of active immune cells (lymphocytes) in the brain and spinal cord. While teriflunomide is usually well- tolerated, there are some side effects which must be considered.

- **Teriflunomide is teratogenic,** meaning it can cause malformations of a fetus. Both females and males planning to have children should be counseled to avoid pregnancy while on this medicine. In addition, the medicine stays in the system for up to 2 years after stopping dosing, so a specific program to remove the medicine from the system has to be followed for two weeks in those patients planning to start a family.
- **Liver injury** has been reported with leflunomide, a related compound used for rheumatoid arthritis. While this has not been seen with teriflunomide, having liver tests before and after beginning teriflunomide is prudent.
- **Other side effects** which may be seen with teriflunomide include: influenza-like symptoms, diarrhea, nausea, and paresthesias (tingling or numbness). In clinical trials. 2% of patients developed a neuropathy, a disorder of peripheral nerve function usually causing tingling or numbness in the feet and hands.

Dimethyl fumarate (Tecfidera)

Dimethyl fumarate (DMF) (Tecfidera) was approved by the FDA in 2013 for relapsing forms of MS. This medicine also reduced the frequency of relapses of MS, as well as reduced MRI activity and progression of MS.

The exact mechanism of action is not known, but the medicine may inhibit some pathways which lead to more inflammation. DMF is an oral agent administered as a twice-a-day 240-mg dose pill. A seven-day starter pack of 120-mg pills is available and recommended to help improve tolerability. The medicine may be tolerated better if taken with food.

Dimethyl fumarate is generally safe and well tolerated. It can lower lymphocyte count, so a blood count (CBC and diff) before starting and a few months after starting is recommended to monitor this. Two main side effects may be seen with DMF:

- **Skin flushing.** Although uncommon, when it is seen, skin flushing typically occurs 30 minutes to several hours after taking DMF. Itching and redness are sometimes reported, too. A placebo-controlled study found that aspirin can significantly reduce flushing.
- **Gastrointestinal symptoms** may occur, including diarrhea, nausea, abdominal pain, and vomiting. Symptoms are most common in the first few weeks after starting DMF and typically reduce significantly by one month of treatment. Symptomatic therapies can be used in patients, where needed, including H2 proton pump inhibitors, metoclopramide, bismuth subsalicylate, loperamide, as needed depending upon the gastrointestinal symptoms.
  Although DMF is a potent immunomodulatory drug and reversibly lowers blood lymphocyte counts, the clinical trials did not observe an increased rate of either routine infections or opportunistic infections. However, there are reports of progressive multifocal leukoencephalopathy (PML) with another fumaric acid preparation (Fu- maderm®), which is available in Germany.

Specific information on each of these medicines can be found at the following websites:

Fingolimod (Gilenya) www.gilenya.com

Teriflunomide (Aubagio) www.aubagio.com

Dimethyl fumarate (Tecfidera) www.tecfidera.com

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