National Multiple Sclerosis Society
Greater New England Chapter

MS Progress Notes...

A newsletter for health professionals
Volume 9, Number 2 Spring 2014

Update on Oral Medications For Multiple Sclerosis

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Introduction. Oral medicines represent a major breakthrough in caring for patients with multiple sclerosis. A major shift in the treatment landscape is under way as many patients previously managed with injectable therapies are switching to oral therapy and some newly diagnosed patients are starting therapy with a pill rather than an injectable. While it is understandable that patients would be eager to swallow a pill rather than administer an injection, one must tailor therapy for each patient. There are important risks and benefits with each pill that need to be weighed with each patient's comorbidities and medications.

Dimethyl fumarate (Tecfidera®) is a pill that is taken twice each day and in two clinical trials, reduces relapse rates compared to placebo by about 53%[1] and 44%[2] respectively. It may take several months for the differences between treatment groups to become apparent, so for patients with recently active disease, monthly doses of methylprednisolone 1g IV q month for 3-6 months may be warranted. Between those trials, there was inconsistent data as to whether there was a difference in disability progression over two years. The precise mechanism of action of Tecfidera is not clear, but it does have anti-inflammatory and anti-oxidant effects in part mediated by the Nrf2 pathway. Tecfidera is approved for relapsing forms of MS, and is administered at 120mg twice a day for one week, and then escalation to maintenance dosage 240mg twice a day. A complete blood count is required prior to starting. Flushing, nausea, cramping and diarrhea may occur at treatment initiation or at escalation to higher dosages, but these side effects largely subside after the first month. We generally recommend that patients take the medication with food and otherwise use a symptom-based approach for mitigating side effects. For flushing, ASA 81mg PO daily can help. Stomach upset can respond to Pepto Bismol, which also contains salicylates. Some patients with diarrhea respond to Lomotil. Tecfidera is classified as Pregnancy category C, and breast-feeding on treatment is not recommended.

Fingolimod (Gilenya®) is a 0.5mg pill taken once daily and prevents 55% of relapses compared to placebo in one clinical trial[3]. When compared to Avonex, fingolimod-treated patients had 48% fewer relapses over one year[4]. Fingolimod works by keeping white blood cells (that fight infection and cause MS) trapped in lymph nodes through modulation of the sphingosine-1 phosphate receptor. There are some safety concerns that are largely covered by the extensive testing required to start therapy including VZV primary exposure, bradycardia & atrioventricular conduction block with the first doses, macular edema, elevated liver-enzyme levels, and mild hypertension. Because of transient bradycardia, which was symptomatic in 5 of 19 cases reported in the pivotal trials where 1703 patients received Gilenya, a 6-hour monitoring period is required at the time of first dose administration and is generally performed in the outpatient neurologist's office, although some situations may warrant inpatient monitoring. The cardiac effects of Gilenya are short-lived, as the sphingosine receptors on cardiac myocytes are internalized with ongoing exposure. Nevertheless, patients with cardiac disease or other medications that slow AV nodal conduction or cause prolongation of the QT interval might consider a different option, or hold those medications while starting fingolimod. Fingolimod is categorized as pregnancy category C, and should not be used during breast-feeding.

Teriflunomide (Aubagio®) is a daily pill that is available in two doses, 7mg and 14 mg. At the higher dose, it prevents 31.5% of relapses and does slow progression of disability compared to placebo[5]. The lower dose has a similar effect on relapses but does not have a significant effect on disability. This medicine slows production of nucleic acids via the salvage pathway, required for rapid white blood cell proliferation. Prior to starting the medicine, one must test negative for pregnancy and exposure to tuberculosis. The medicine has a black box warning for teratogenicity (pregnancy category X) and should not be given during breastfeeding. There are also rare cases of liver damage that prompted need for six months of monthly liver function testing. Furthermore, 13% of patients experience several months of hair thinning that is reversible, although this can be a concern for those with thin hair. Another concern is that the medication has a long half-life and in the event that there is a teriflunomide-related adverse event, some patients must undergo an "accelerated elimination procedure" involving cholestyramine washout usually given at a dose of 8g three times daily for 11 days.

Choosing the right medicine. With three new options in the

last three years, patients might ask how one approaches picking the best medicine for each patient. For patients having breakthrough disease from an injectable firstline agent, and patients who cannot tolerate an injectable, these medicines will be most helpful. In general, given the strength of the relapse reduction versus their respective placebo groups, one might lean toward dimethyl fumarate and fingolimod as more efficacious agents. However, the relative efficacy of these agents cannot be determined with confidence until they are directly compared to one another within the same blinded trial. Deciding between dimethyl fumarate, teriflunomide and fingolimod can be tricky but medical co-morbidities and medicines can be helpful. Patient preference for a daily dosing regimen can sway some patients. Some patients who are eligible for any of these therapies ask, "which is better?" It is not possible to offer an iron-clad argument that either medicine is indeed stronger. One approach that some find valid is that fingolimod was shown to prevent more relapses than Avonex while dimethyl fumarate did not demonstrate superiority over Copaxone. For patients with less active disease who are tolerating their injectable medicine, one can easily justify staying on an injectable medicine. The rationale is that with the recent placebo group relapse rate of 0.4 relapse/year, one would need to treat a patient for ten years with Tecfidera or Gilenya in order to prevent a single relapse as compared to treatment with an injectable medicine. For patients with frequent relapses, this math does favor more efficacious medicines and justifies the risks associated with these oral medicines.

Family Planning. Women in their childbearing years should be counseled to use reliable forms of contraception as Tecfidera and Gilenya are FDA Pregnancy Category[6] C – "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks." Aubagio is FDA Pregnancy Category X – "Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits."

Patients with Positive JCV Serology. It is common for patients to be started on oral medicines after testing positive for JCV exposure. The JCV serologic test has been shown to determine risk of developing progressive multifocal leukoencephalopathy (PML) in patients treated with Tysabri[7]. Data concerning PML risk with these new oral agents is limited. For example, of 70,000 patients treated with fingolimod, there has been a single reported case of PML that is under investigation. With Tecfidera, there have been no reported cases of PML. With a related medicine called Fumaderm, which contains the active ingredient of Tecfidera, there are rare cases of PML in patients with past exposure to immunosuppressive medicines and long-standing low white blood counts from Fumaderm. The FDA is aware of these cases and approved Tecfidera without a black box warning. While the risk of PML with these agents is not zero, it is most likely lower than the 3.3/1000 risk of PML with natalizumab[8].

Patients with Progressive MS. These medications are approved for patients with relapsing forms of multiple sclerosis (which can include patients with SPMS). Whether these treatments impact "progressive disease" is unknown. While it is rare, patients can suffer relapses late in their disease course. A study of Gilenya in PPMS patients is underway[9].

Conclusion. Oral medicines offer several exciting treatment options for some MS patients. Many patients will benefit from making a switch, but while selecting an agent, clinicians must be mindful of the patient's medications, co-morbidities and the side effects of the oral agent. Informing patients about the risks and benefits of each medication including potential fetal risk and PML is essential. Some patients would do well to remain on their injectable medication as these medications are both safe and efficacious. Despite some safety concerns, the oral medicines do offer much improved ease of medication administration, and in some cases, an increase in efficacy from injectable medicines.

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