Mellen Center Approaches: Use of DMF in MS (Tecfidera)

Q: What is dimethyl fumarate and how does it work?

A: Dimethyl fumarate (DMF, Tecfidera) was approved by the US FDA in March 2013 as an oral disease modifying treatment for relapsing forms of MS. Combined data from a Phase II study and two Phase III trials showed that DMF reduces relapses, disability progression, MRI lesion activity.

The exact mechanism of action of DMF is not known, but may include direct inhibition of proinflammatory pathways and effects on dendritic cell differentiation. DMF may also act through the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) antioxidant response pathway.

Q: How is DMF administered?

A: DMF is administered as a single 240mg capsule, twice per day (once in the morning and once in the evening; it does not need to be taken exactly 12 hours apart). A seven-day starter-pack of 120 mg capsules twice per day is available and recommended to help improve tolerability. Food does not alter DMF's absorption. Therefore, DMF can be taken without regard to meals, although gastrointestinal tolerability may be improved by taking it with food. Missed doses should be skipped and do not need to be made up. However, if a few days are missed, patients may have a recurrence of their side effects.

Q: For whom should DMF be considered?

A: DMF was approved to treat relapsing forms of MS. DMF is also an appropriate treatment option for patients with ongoing disease activity, intolerable side effects, or logistical issues with other MS therapies.

Q: May DMF be used as initial MS therapy?

A: DMF is approved as first line therapy (i.e. patients are not required to have tried other medications before DMF), although long-term experience with its use is limited. Note that some insurances will not approve this as first line therapy but may insist that patients uses other medications first. We often have patients check with their insurance before beginning the paperwork for DMF.

Q: Should patients switch from a previously-available injected medication to DMF?

A: We anticipate many patients currently on an injectable therapy will be attracted to DMF's oral route of administration. However, if a patient is stable clinically and radiographically, and

he/she is not experiencing significant adverse effects, in general, we recommend not switching therapy.

For JC virus antibody-positive patients on Tysabri who are concerned about the risk of progressive multifocal leukoencephalopathy, DMF is a reasonable consideration.

As with anyone on an MS medicine, we do consider switching medicines in the following situations:

1. Intolerance or specific side effects of present medicine.
2. Risk of major side effects such as PML with present medicine
3. Break through disease:
    a. Continued relapses above 'acceptable' level of activity (there are no well-defined criteria but more than one relapse per year or functionally meaningful relapses often prompt us to change medicine)
    b. Continued MRI activity (New T2 lesions or enhancing lesion). Again there is some low level of new disease activity which would be expected on all of the medicines and a judgment call is necessary to decide when a change makes sense.

Q: What side effects and safety issues does DMF have?

A: DMF is generally safe and well tolerated. DMF typically lowers the lymphocyte count. The FDA recommends a complete blood count prior to initiating treatment, and then again annually and when clinically indicated.

The main side-effects of DMF are skin flushing and gastrointestinal symptoms.

Skin flushing: Although uncommon, when it is seen, skin flushing typically occurs 30 min to several hours after taking DMF. Pruritis and erythema are sometimes reported, too. A placebo-controlled study found that aspirin can significantly reduce flushing.

Gastrointestinal symptoms: diarrhea, nausea, abdominal pain, vomiting can be seen between 30 min and several hours after taking DMF. 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. The enteric formulation of DMF makes it mostly like to be absorbed in the intestines. Accordingly, patients who have received gastric bypass are not expected to have altered tolerability.

Some patients have reported benefit for the GI symptoms using an anecdotal list of foods: peanut butter, chocolate milk, olive oil, almonds, cashews, 'Fritos', or avocados.Q: Can the dosing schedule be changed to reduce the risk of GI side effects?

Different dosing strategies have been applied to try to reduce GI side effects. At the Mellen Center we have been using the following modification of the dosing strategy for DMF:

First two weeks: DMF 120 mg twice a day
Third and fourth week: DMF 240 mg with largest meal, and one 120 mg with opposite meal (breakfast and dinner).
After fourth week: DMF 240 mg bid with meals.

An alternative regimen tested by NYU medical center (presented ACTRIMS meeting Sept 2014):

First two weeks DMF 120 mg once a day with meal
Second two weeks DMF 240 mg once a day with meal
After 4th week: DMF 240 mg bid with meals.

Q: Is there a risk of PML with DMF and if so how do I risk stratify and monitor appropriately?

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. This decline in the lymphocyte count tends to progress over the first year of treatment and counts remain low throughout the course of treatment. However, lymphocyte counts can be quite variable over time, too. Lymphocyte counts may take from 12-16 weeks to return to normal after treatment with tecfidera.
There have been case reports of progressive multifocal leukoencephalopathy (PML) with another fumaric acid preparation (Fumaderm), which is available in Germany. Most of these cases were on another immune suppressing medication prior to or at the time of DMF therapy, or had persistently low lymphocyte counts.

In October 2014 a single case was reported with DMF of PML which was fatal. This patient was enrolled in ongoing clinical trials of DMF and had not been on immunosuppressive medications prior to this trial. The patient experienced persistently low absolute lymphocyte counts for 3.5 years of treatment (<500), and was not recognized as having PML until late in the disease course.

On the basis of this case, at the Mellen Center we now recommend a CBC with differential every 6 months while patients are on dimethyl fumarate. In addition:

If absolute lymphocyte counts are 500-750, we recheck in 3 months then every 3 months until the count rises above 750

If the absolute lymphocyte count is under 500, we recheck CBC monthly and obtain JCV serology.
If the absolute lymphocyte count is persistently <500 and the patient is JCV seropositive, we consider an alternative treatment.

Q: How long should a patient wait after stopping another disease modifying therapy before starting DMF?

A: There is no data regarding optimal wash-out times. The theoretical increased risk of complications from incomplete wash-out from the previous therapy needs to be balanced against the risk of return of MS disease activity during a wash-out period. In some patients, the return of disease activity can be very severe. Decisions regarding wash-out are influenced by the treatments and the patients underlying disease activity.

We have adopted the following wash-out periods before starting DMF:
Interferon, glatiramer acetate, and teriflunomide: No washout period
Fingolimod: 2-3 week wash-out (so that lymphocyte counts normalize)
Natalizumab: No wash-out period
Corticosteroids: No washout period

Q: What testing is required prior to DMF therapy?

A: Prior to therapy, a complete blood count (CBC) is recommended.
We have also begun to do JCVirus antibodies on patients starting natalizumab, fingolimod, or dimethyl fumarate due to the case reports of PML on the latter two medications and due to the known propensity of natalizumab to case PML.

Q: Are there any restrictions on who can take DMF?

A: There are no contraindications for using DMF. Patients with nausea and diarrhea at baseline should use DMF with caution, as it may aggravate those symptoms.

Q: Does DMF need to be stopped for surgery?

A: There are no reports of complications related to surgery in patients receiving DMF, so we do not recommend stopping DMF for surgery.

Q: Does the risk of infection relate to peripheral blood white blood cell or lymphocyte counts?

A: There is no clear relationship between the level of lymphocyte reduction and the incidence (or severity) of infections. See above discussion of risk mitigation for PML.

Q: Is DMF effective in progressive MS?

A: The effectiveness and safety of DMF in primary and secondary progressive MS is not known.

Q: Is DMF safe during pregnancy?

A: Based on animal studies, DMF potentially causes fetal harm and is classified as Pregnancy Category C. Women should use effective contraception while taking DMF and for some time after stopping it. Women should discontinue DMF prior to attempting to become pregnant. There is no known effect of DMF on sperm.

Q: Can DMF be used in combination with other MS disease therapies?

A: There are no data concerning the safety or utility of combining DMF with other MS disease therapies. Co-administration of DMF with immunosuppressant medications would be expected to increase the risk of infection.

Q: Can DMF be combined with MS symptom medications?

A: DMF can be combined with MS symptom medications without problem. There are no specific medications which are contraindicated while patients are on DMF.

Q: Can DMF be combined with medications for other conditions?

A: There are no medications known to interact with DMF.

Q: Can the dose of DMF be increased beyond 240 mg twice daily?

A: The approved dose of DMF is 240 mg twice daily (480 mg total per day). 240 mg thrice daily (720 mg total per day) were tested in the DMF Phase II and Phase III trials, but there was no greater efficacy at this dose. Lower doses of DMF (i.e. 240 mg once daily) have not been evaluated and so are not currently recommended.

REFERENCES

1. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367:1098-107.
2. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367:1087-97.