Dimethyl Fumarat – a New Player in Oral Treatment Options for Relapsing Forms of Multiple Sclerosis

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One of the latest oral treatment options for relapsing forms of multiple sclerosis is dimethyl fumarat, approved by FDA on February 2013 and by EMA on January 2014 (1, 2).

The mechanism of action of dimethyl fumarat (DMF) in multiple sclerosis is not completely understood. DMF and its active metabolite, monomethyl fumarate (MMF) has been shown to activate the nuclear factor (erythroid-derived)-like 2 (NrF2) pathway in vitro and in vivo in animals and humans. The NrF2 pathway is involved in the cellular response to oxidative stress and regulates “antioxidant” genes involved in protecting cells from damage (2, 3).

One of the phase II study published in The Lancet about the investigational product oral fumarat (BG 00012) has shown that this treatment reduced annualised relapse rate by 32% and had a favorable safety profile for dose of 240 mg x 3 daily (4). The study was a randomized, double-blind, placebo-controlled trial and comprised 257 patients recruited in 43 centres. The trial had 4 arms for randomization (1:1:1:1) - placebo, BG 00012 120 mg/day, 360 mg/day and 720 mg/day for 24 weeks, and after that only three active arms for more 24 weeks. The mean EDSS score was below 3 for all 4 trial arms (4).

The next two phase III studies were CONFIRM and DEFINE, published in New England Journal of Medicine on September 2012.

The CONFIRM study (5) was a randomized, multicenter, double-blind trial to evaluate the efficacy and safety of BG-12 at a dose of 240 mg two or three times per day versus placebo and a reference comparator (glatiramer acetate). The study enrolled 1430 randomly assigned patients in 200 sites in 28 countries. At 2 years, the relative reductions of the annualized relapse rate were 44% for twice-daily BG-12 (p<0.001), 51% for thrice-daily BG-12 (p<0.001) and 29% for glatiramer acetate (p=0.01). Reductions in disability progression were not significant in all of three active arms. Most frequent adverse events were flushing and gastrointestinal problems for BG-12 and injection-related skin reactions for glatiramer acetate. Lymphocyte counts decreased in active treatment arms with BG-12.

The DEFINE study (6) was a randomized, double-blind, placebo-controlled phase III trial to determine the efficacy and safety of oral BG-12 – in two active arms: 240 mg x 2 daily and 240 mg x 3 daily – versus placebo. A total of 1237 were randomized and a total of 952 patients completed the study (77% in each arm of BG-12). The mean duration of participation was almost 84 weeks for all three groups. The
annualized relapse rate at 2 years had a significant relative reduction of 53% and 48% with the two BG-12 regimens (p<0.001). Oral BG-12 significantly reduced the number of gadolinium-enhancing lesions and of new or enlarging T2-weighted hyperintense lesions for both regimen of BG-12. Adverse events reported during the study were flushing and gastrointestinal events decreased lymphocyte counts and elevated liver enzymes levels.

On March 27, 2013, U.S. Food and Drug Administration approved dimethyl fumarate capsules to treat adults with relapsing forms of multiple sclerosis. FDA recommends to monitor white blood cell count before starting treatment and annually thereafter. The most common adverse reactions reported by patients are flushing and stomach problems (nausea, vomiting, diarrhea) (1).

On January 30, 2014, European Medicines Agency (EMA) approved for use of dimethyl fumarate in the European Union for adults with relapsing-remitting multiple sclerosis. Dimethyl fumarate is available as oral capsules (120 and 240 mg) to be taken with food. The dose is 120 mg twice a day for the first seven days, after which it is increased to 240 mg twice a day (2).

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