Dimethyl Fumarate: an Investigational Drug for Relapsing/Remitting Multiple Sclerosis

Some main pathologic factors of multiple sclerosis (MS) include inflammation and oxidative stress. Oral dimethyl fumarate slows MS disease progression through its anti-inflammatory and cytoprotective properties. A randomized, double-blind, placebo-controlled study assessed the efficacy of dimethyl fumarate in treating relapsing/remitting MS in 1234 patients.

Patients were 18-55 years old and were considered ambulatory (EDSS [Expanded Disability Status Scale] score ≤5). Patients were excluded if they had a progressive form of MS, another major disease, abnormal lab tests, or a recent exposure to contraindicated medication. The patients were randomly given either dimethyl fumarate 240 mg twice daily (BID), dimethyl fumarate 240 mg three times daily (TID), or placebo for two years. The primary endpoint was the proportion of patients who had a relapse by two years. Secondary endpoints included the annualized relapse rate (number of relapses divided by the number of patient-years in the study) and the time to disability progression. Nine hundred fifty-two patients completed the study, with similar proportions of patients in each group. Baseline characteristics were similar between groups. The proportion of patients who experienced at least one relapse at two years was significantly less in the dimethyl fumarate groups (27% in the BID group, 26% in the TID group, and 46% in the placebo group; \( p=0.001 \)). Both dimethyl fumarate BID and TID significantly decreased the risk of relapse by 50% (HR for BID group 0.51, 95% CI 0.40-0.66; HR for TID group 0.50, 95% CI 0.39-0.65). The annualized relapse rates at two years were 0.36, 0.17, and 0.19 in the placebo group, BID group, and TID group, respectively. These annualized relapse rates represented 53% and 48% relative reductions in the BID and TID groups, respectively (\( p<0.001 \)). Progression of disability occurred in 27% of the placebo group, 16% of the BID group, and 18% of the TID group. Dimethyl fumarate BID reduced the risk of disability progression by 38% compared to placebo (HR 0.62, 95% CI 0.44 to 0.87; \( p=0.005 \)). The risk of disability progression was reduced by 34% in the TID group compared to placebo (HR 0.66, 95% CI 0.48 to 0.92; \( p=0.01 \)). Adverse events were minimal, although flushing and gastrointestinal events were the most prevalent in the dimethyl fumarate groups in the first month. The adverse events leading to discontinuation were similar in all three groups. The authors concluded that dimethyl fumarate significantly reduced the proportion of patients who had a relapse by two years and the annualized relapse rate compared to placebo. Because this study only included patients who had relapsing/remitting MS, the results may not be generalizable to other forms of MS.

CONCLUSION: Dimethyl fumarate is an oral MS medication that decreased relapse rates, annualized relapse rates, and the risk of disease progression compared to placebo in patients with relapsing/remitting multiple sclerosis.


By Karri Sundgren, Pharm.D. Candidate
Myrbetriq™ (mirabegron) for Overactive Bladder

Inappropriate contraction of bladder muscles can lead to overactive bladder (OAB), which is traditionally treated with behavioral therapies and antimuscarinic medication. Recently, three studies have shown that Myrbetriq (mirabegron; approved on June 28, 2012) might be a good option for OAB because of its unique mechanism of action as a beta-3 agonist. The beta-3 adrenoceptor subtype is thought to predominantly mediate the bladder’s smooth muscle relaxation.

A multicenter, double-blind, randomized, placebo-controlled study found that mirabegron reduced the symptoms of OAB more than placebo. Patients (89.3% female) were at least 18 years old and had OAB for ≥3 months. OAB was defined as having ≥8 micturitions in 24 hours and ≥3 urgency issues with or without incontinence during a three-day period. Patients were randomized to receive either placebo (n=166) or mirabegron 25 mg (n=167), 50 mg (n=167), 100 mg (n=168), or 200 mg (n=166) daily for 12 weeks. The primary endpoint was the change from baseline in the number of micturitions in 24 hours. Secondary endpoints included volume voided per micturition and urgency incontinence episodes. These outcomes were measured using patient micturition diaries. The average number of micturitions in 24 hours decreased significantly in the 50 mg (-2.1), 100 mg (-2.1), and 200 mg (2.2) groups compared to placebo (-1.4; p=0.05). Volume voided per micturition was significantly greater in the 50 mg (27.3 mL), 100 mg (25.6 mL), and 200 mg (33.3 mL) groups compared to placebo (7.3%; p=0.05). Urgency incontinence episodes significantly decreased in the 25 mg (-1.3), 50 mg (-1.1), 100 mg (-1.2), and 200 mg (-1.2) groups compared to placebo (-0.4; p=0.05). The occurrence of adverse events was similar between all the groups (43%). The most common adverse events were infection, infestations, and gastrointestinal disorders. The authors concluded that mirabegron was safe and effective in reducing micturitions and urgency incontinence episodes and increasing micturition volume at doses of 50 mg-200 mg.

Another multicenter, double-blind, randomized, placebo-controlled trial found similar results.

A third multicenter, double-blind, randomized, placebo-controlled study found that mirabegron reduced the symptoms of OAB more than placebo. Patients (72.2% female) were at least 18 years old and had OAB ≥3 months. Patients were randomized to receive either placebo (n=494), mirabegron 50 mg (n=493), mirabegron 100 mg (n=496), or tolterodine SR 4 mg (n=495) for 12 weeks. The primary endpoints were the changes from baseline in the average number of incontinence episodes and micturitions in 24 hours. The secondary endpoint was the volume voided per micturition. The number of incontinence episodes in 24 hours was decreased by -1.57, -1.46, and -1.27 in the 50 mg, 100 mg, and tolterodine groups, respectively, compared to the placebo group (-1.17; p=0.05 for mirabegron groups vs. placebo). There were fewer micturitions in 24 hours in the mirabegron and tolterodine groups compared to the placebo group (-1.93 in the 50 mg group, -1.77 in the 100 mg group, -1.58 in the tolterodine group, and -1.34 in the placebo group; p<0.05 for mirabegron groups vs. placebo). All of the active groups showed significantly more volume per micturition than the placebo group (24.1 mL in the 50 mg group, 25.5 mL in the 100 mg group, 25.0 mL in the tolterodine group, and 12.4 mL in the placebo group; p<0.05 for all groups vs. placebo). The occurrence of adverse events was similar between groups. The authors concluded that mirabegron was superior to placebo in improving important OAB symptoms.

The results of these studies are limited because of the subjective nature of the data recording (patient journals). The results may not be generalizable to male populations because these trials enrolled mostly women. Published information for these trials is only available in abstract form, so details of the studies are not available for critique.

The usual dose of mirabegron for OAB symptoms is 50 mg a day. The most common adverse effects are headache, hypertension, nasopharyngitis, and urinary tract infections.

In conclusion, mirabegron is more effective than placebo in treating common and significant OAB symptoms and may be an alternative therapeutic agent for those intolerant to antimuscarinic medications.

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Efficacy of Homeopathy

Many patients utilize complementary and alternative medicine (CAM), including homeopathy. The widespread use of homeopathic medicine has been a motivator for medical schools around the world to include CAM in their curriculum.\textsuperscript{1,4} Although public acceptance of homeopathy is high, a challenge for the CAM curricula is that homeopathic treatments may not be able to withstand the critical analysis required by evidence-based medicine.\textsuperscript{4}

Homeopathy is based on the idea that “like cures like”.\textsuperscript{5,5} An issue with homeopathy is the extensive dilution performed to formulate the treatment. Diluting an agent to increase its potency is contrary to the principles of pharmacodynamics. An increased concentration of a substance usually corresponds with an increased reaction. The amount of dilution commonly employed in homeopathic treatments does not allow for the initial ingredient to remain in the solution.\textsuperscript{5}

An analysis that compared 110 placebo-controlled homeopathy trials with 110 disorder- and outcome-matched conventional-medicine trials found weak evidence for a specific effect of homeopathy and strong evidence for specific effects of conventional medicine.\textsuperscript{6} The included trials were randomized and placebo-controlled, had clinical outcomes, and had a median size of 65 participants. Outcomes included in the analyses were the main outcome measures, patients’ and physicians’ overall assessment of improvement, and the most clinically relevant outcome (e.g., occurrence or duration of an illness). Smaller, lower quality trials showed more beneficial effects than large, high-quality trials. Odds ratios <1.0 indicated a beneficial effect of treatment. When the analysis only contained higher quality studies, the OR for homeopathy was 0.88 (95% CI 0.65-1.19) and 0.58 (95% CI 0.39-0.85) for conventional medicine, indicating a greater benefit for conventional medicine. Investigators concluded that when analyses were restricted to large trials of higher quality, there was no convincing evidence that homeopathy was superior to placebo, and that conventional medicine’s beneficial effect persisted.\textsuperscript{6}

Publication bias may have influenced the results of these analyses, and the majority of the trials included in the analyses were of methodologically poor quality. Both of these factors may have led to an overestimation of the positive effects associated with homeopathy.\textsuperscript{1,2}

Attempts to assess the clinical effects of homeopathy with placebo-controlled trials only seems to increase the controversy surrounding homeopathy. Although most study outcomes show a homeopathic effect slightly greater than placebo, no definitive outcome in any one condition has been clinically proven or disproven. The increased use of homeopathic therapy by patients precipitates the need for health care professionals to be aware of these types of treatments.

By Celeste Norris, Pharm.D. Candidate

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A contaminated compounded methylprednisolone acetate product has led to a recent outbreak of fungal meningitis in patients who received epidural injections with the medication. As of December 4, 2012, there have been 541 cases of meningitis (36 fatal cases) in 19 states. The drug compounding center has distributed about 17,700 doses of methylprednisolone acetate to 23 different states since May 21, 2012, and about 14,000 of those doses have been administered to patients. Since the outbreak, the NECC has voluntarily recalled all of their products.

A sample of cerebrospinal fluid is necessary to diagnose this disease, and a lumbar puncture is recommended to those exposed patients as soon as they start to show symptoms. Patients who may have been exposed should be closely monitored for symptoms, and treatment should be started when infection is evident in the cerebrospinal fluid sample. Treatment for Exserohilum meningitis is not well defined, but currently the CDC is recommending two strong antifungal agents, voriconazole and amphotericin B. Voriconazole is indicated for Aspergillus infections and, based on published literature, should be effective for black-brown molds like Exserohilum. First-line treatment at this point is voriconazole twice a day (either IV or oral). Liposomal amphotericin B is also indicated for Aspergillus and should be added if a patient has very severe symptoms at presentation or is not improving, or is getting worse, on voriconazole alone. The optimal duration of therapy is unknown, but at least three months of treatment is recommended. Longer treatment is recommended if there are complications associated with the infection. Prophylactic treatment for those exposed, or treatment for patients with negative lumbar punctures, is not recommended at this time.

The CDC, together with local health departments, is continuing to investigate this multistate outbreak of fungal meningitis. Healthcare providers should continue to watch for symptoms of infection in those who have received an epidural injection of this compounded methylprednisolone product. More information on the outbreak and fungal meningitis treatment can be found on the CDC website: http://www.cdc.gov/hai/outbreaks/clinicians/index.html#Guidance.

By Amy Wetch, Pharm.D. Candidate

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Myrbetriq™ (from page 2)

Literature Highlight: Hydrocodone/Acetaminophen for Pain Control in Surgical Abortion

Despite a recent Cochrane review that noted a lack of data supporting oral opioid use in abortion procedures, the World Health Organization recommends adding hydrocodone/acetaminophen to the regimen of ibuprofen and paracervical block. This double-blind, randomized, placebo-controlled study assessed the efficacy of hydrocodone/acetaminophen for pain control during first-trimester surgical abortion.

A total of 121 women, 18 years or older, who were undergoing first-trimester surgical abortion were stratified by gestational age then randomized into the placebo group (n=60) or the hydrocodone/acetaminophen group (n=61). Forty-five to ninety minutes prior to the procedure, patients received oral ibuprofen 800 mg, oral lorazepam 2 mg, and either two tablets of hydrocodone-acetaminophen 5/325 mg or two tablets of placebo. Patients received a standard paracervical block after speculum placement. Procedural pain scores were collected by research personnel using a 100-mm visual analogue scale immediately after each step (speculum insertion, paracervical block placement, dilation, and aspiration). Post-procedure information was collected 30 minutes after speculum removal. Post-procedure information included vital signs, pain, side effects (nausea, sleepiness, and pruritus), satisfaction, and whether or not participants believed they received the active drug or a placebo. The primary endpoint was patient pain during aspiration.

Despite stratification, no benefit of pain control during aspiration or post-procedure was observed with the use of hydrocodone/acetaminophen compared to placebo. The mean visual analogue scale score during aspiration was 65.9 mm for the hydrocodone/acetaminophen group and 63.2 mm for the placebo group (p=0.59). There was a significant increase in postoperative nausea in the hydrocodone/acetaminophen group compared to placebo (p=0.03). Pain during aspiration was significantly associated with nervousness about procedure, nervousness about pain, and expected pain (p=0.01, p=0.01, p=0.04, respectively). Hispanic patients were also more likely to experience pain during aspiration (p=0.02). The subjective nature of pain creates a challenge for a study evaluating pain control medications. Lorazepam use as well as limiting post-procedural evaluation to 30 minutes also creates limitations for this study.

CONCLUSION: Hydrocodone/acetaminophen use did not decrease pain more than placebo during first-trimester abortion procedures.


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