**Literature Highlight:**

Fidaxomicin Versus Vancomycin for *Clostridium difficile* Infection

*Clostridium difficile* infection can cause symptoms ranging from diarrhea to life-threatening inflammation of the colon. Infection incidence in the United States is increasing, and severity is worsening with the emergence of a hypervirulent strain (NAP1/BI/027). Currently accepted treatments include oral metronidazole and vancomycin. This multicenter, double-blind, randomized, noninferiority trial compared a new macrocyclic antibiotic, Dificid™ (fidaxomicin), to vancomycin in the treatment of *C. difficile*.

Patients with a *C. difficile* infection (confirmed by the presence of diarrhea and *C. difficile* toxin A and/or B) were randomly assigned to receive either oral vancomycin 125 mg every six hours (n=327) or oral fidaxomicin 200 mg every 12 hours with intervening placebo doses matching the vancomycin schedule (n=302) for a total of 10 days. The primary endpoint was clinical cure, defined as the resolution of diarrhea for the duration of therapy and no further need for pharmacotherapy. Secondary endpoints were the rate of recurrence of *C. difficile* infection (re-emergence of diarrhea within four weeks after the last day of therapy) and global cure (resolution of diarrhea with no recurrence).

Baseline characteristics were similar between groups. Based on an intent-to-treat analysis, there was no difference in clinical cure rates between fidaxomicin and vancomycin (88.2% vs. 85.8%, respectively; no p-value reported). However, fidaxomicin had a lower rate of recurrence than vancomycin (15.4% vs. 25.3%; p=0.005). Additionally, fidaxomicin demonstrated a higher incidence of global cure than vancomycin (74.6% vs. 64.1%; p=0.006). Patients taking fidaxomicin had a significantly higher rate of dizziness and rash than those taking vancomycin (dizziness 4.0% vs. 1.2%; p=0.0405; rash 3.0% vs. 0.6%; p=0.0315). Investigators considered all 12 cases of dizziness to be mild and 4 of the cases to be related to the study medication. None of the rash cases were determined to be related to either of the study medications. There was a significantly higher rate of laboratory abnormalities (elevated AST/ALT, hyperuricemia) in the fidaxomicin arm (4.7% vs 1.2%; p=0.0148). Investigators considered only 3 of the 14 cases of laboratory abnormalities to be related to fidaxomicin, and these were considered mild elevations. The authors concluded that fidaxomicin and vancomycin had similar effectiveness in treating *C. difficile* infection but fidaxomicin may be better at preventing recurrence. The study duration was possibly insufficient to determine true recurrence rates in both groups. Additionally, power was not addressed, and potential bias exists because the fidaxomicin manufacturer funded the study and performed the statistical analysis.

**SUMMARY:** Fidaxomicin and vancomycin had similar effectiveness in the treatment of *C. difficile* infection. Although fidaxomicin was superior to vancomycin in preventing infection recurrence, it was associated with more adverse effects.


*By Sadie Linford, Pharm.D. Candidate*
Potiga™ (ezogabine) is a new antiepileptic drug (AED) that was approved on June 10, 2011. Although approval of ezogabine was originally denied based on urinary adverse drug reactions, new studies have shown that these reactions occurred similarly with placebo and that they were reversible upon ezogabine discontinuation. Ezogabine possesses a novel mechanism of action which involves augmenting the potassium channels KCNQ2 and KCNQ3 and keeping them open for a prolonged period of time, which minimizes seizure activity. Ezogabine also interacts with GABA, which slows the production of neuroactive proteins. The following studies examine its efficacy and safety in partial-onset seizures.

A randomized, double-blind, placebo-controlled trial evaluated the efficacy and tolerability of ezogabine in the treatment of partial-onset epilepsy. Patients 18 to 75 years old with location-related epilepsy, who were taking between one and three AEDs, and who had four or more seizures in a 28-day period were randomized to receive either ezogabine 200 mg (n=181), ezogabine 300 mg (n=179), or placebo (n=179) three times daily for 12 weeks. Ezogabine was started at 100 mg three times daily and was increased by 150 mg/day each week until reaching a target dose of either 600 mg/day or 900 mg/day. For 12 weeks, patients made daily recordings of their seizure activity in diaries. The primary outcome was the change in seizure frequency in a 28-day period. A secondary outcome was the responder rate (defined as a ≥50% reduction in seizure frequency in a 28-day period). Changes in seizure frequency were significantly different between the two ezogabine groups and placebo (27.9% reduction with ezogabine 600 mg/day, p=0.007; 39.9% reduction with ezogabine 900 mg/day, p<0.001; and 15.9% reduction with placebo). Responder rates were also higher in both ezogabine groups than placebo (38.6% for ezogabine 600 mg/day, 47.0% for ezogabine 900 mg/day, and 18.9% for placebo; p=0.001). The most common adverse events associated with the study drug included dizziness (7%), somnolence (10%), and headache (15%). Weight gain of about 1.0 kg per patient was also noted in both ezogabine groups. Due to the association with urinary symptoms found in previous studies, patients were questioned on all urinary changes. Three patients from the ezogabine groups stopped the study due to urinary issues, including urine retention and nephritis. The authors concluded that ezogabine was an appropriate adjunctive treatment for refractory partial seizures. Limitations of this trial included the small sample size, the risk of reporting bias due to the patient-reported seizures, and manufacturer funding for the study.

In conclusion, ezogabine has a novel mechanism of action in treating patients with partial-onset epilepsy, a good safety profile, and efficacy for decreasing the frequency of seizures. Head-to-head studies involving other AEDs are needed in order to better determine where ezogabine fits in the epilepsy treatment algorithm.

By Carly Maloney, Pharm.D. Candidate

References:
Tradjenta® (linagliptin): A New Oral DPP-4 Inhibitor

Linagliptin is an oral DPP-4 inhibitor that is taken once daily and can be taken with or without food. It is only available in the 5 mg dose, and it does not require dose adjustments for the elderly or for patients with hepatic or renal impairment. Common side effects are nasopharyngitis, back pain, and headache.1

In conclusion, linagliptin is well tolerated with a good safety profile. Linagliptin has the advantage of once-daily dosing with a low risk of hypoglycemia and would be useful for patients intolerant to sulfonylureas. Head-to-head trials with the other DPP-4 inhibitors are needed in order to determine how its efficacy compares with them. Long-term studies are needed to further determine its safety profile.

By Beth Cleavenger, Pharm.D. Candidate

References:
Literature Highlight: Azilsartan, a New Angiotensin Receptor Blocker, Compared to Olmesartan and Valsartan

There are many angiotensin receptor blockers (ARBs) used to treat hypertension (HTN). ARBs are very effective at lowering blood pressure (BP) when compared to other antihypertensives and are very well tolerated. Azilsartan medoxomil (AZLM) was approved on February 25, 2011, and is marketed as Edarbi®. AZLM is the eighth ARB on the market.

A randomized, multicenter, placebo- and active-controlled, double-blind study evaluated the efficacy and safety of AZLM compared to olmesartan (OLM), valsartan (VAL), and placebo in the treatment of HTN. Hypertensive patients with a systolic blood pressure (SBP) of 150-180 mmHg and a diastolic blood pressure (DBP) of 130-170 mmHg were enrolled. Female patients not using birth control were excluded. Patients were randomized to receive either placebo (n=154), 40 mg AZLM (AZLM-40; n=40), 80 mg AZLM (AZLM-80; n=285), 40 mg OLM (n=290), or 320 mg VAL (n=282) every morning for six weeks. The primary outcome was the change in 24-hour mean SBP measured by a 24-hour ambulatory BP monitor. Secondary outcomes included changes in clinic BP, which was taken in a clinical setting, and ambulatory DBP. Ambulatory BP readings were performed at baseline and after six weeks, and clinic BP was taken at baseline and at two, four, and six weeks. Another assessment was response rate, defined as the proportion of patients who had a reduction in SBP of ≥20 mmHg SBP and/or a SBP of <140 mmHg at the end of treatment.

A total of 16% of participants dropped out of the study, and reasons for discontinuing included adverse drug reactions (ADRs), protocol violations, and voluntary discontinuation (placebo n=13, AZLM-40 n=23, AZLM-80 n=80, VAL n=28, OLM n=22). Compared to baseline, reductions in SBP during the 24-hour ambulatory period were -0.3 mmHg for placebo, -13.4 mmHg for AZLM-40, -14.5 mmHg for AZLM-80, -10.2 mmHg for VAL, and -12.0 mmHg for OLM (p<0.001 for all comparisons to baseline). The largest reduction in both systolic and diastolic ambulatory BP was in the AZLM-80 group (p=0.05). The reductions in clinic SBP were largest with AZLM-80 (-14.9 mmHg; p<0.001), followed by AZLM-40 (-14.6 mmHg; p<0.001), OLM (-11.4 mmHg; p<0.001), and VAL (-9.5 mmHg; p<0.001) when compared to placebo at the end of six weeks of treatment. Response rates were 58% for AZLM-80, 22% for placebo, and 49% for both VAL and OLM, (p=0.05 for comparisons between AZLM-80 and placebo, VAL, and OLM). Adverse drug reactions included headache (AZLM-40 6.4%, AZLM-80 4.2%, VAL 7.6%, OLM 7.9%, placebo 9.0%) and dizziness (AZLM-40 3.6%, AZLM-80 3.5%, VAL 1.8%, OLM 3.1%, placebo 2.6%). The safety and tolerability of the different medications were not significantly different across the study groups. The authors concluded that AZLM had many advantages over VAL and OLM, including improved BP lowering properties and a high response rate. Limitations of the study include manufacturer funding and differences in the number of drop outs across the groups.

SUMMARY: AZLM is a new hypertensive medication that shows superiority in reducing SBP and DBP when compared to high-dose olmesartan and valsartan. AZLM appears to have a good safety and tolerability profile.