Cardiovascular disease (CVD) is the leading cause of death worldwide in low- and medium-income countries. Risk factors for CVD include hypertension and dyslipidemia. A double-blind, randomized, placebo-controlled trial investigated the effects of a polypill given to adults aged 50-79 years old. The objective was to evaluate the tolerability and effects of a combination therapy on risk factors for CVD, including blood pressure and LDL lipid levels.

Patients from Kalaleh in Golestan Province, Iran (n=1733) attended an assessment clinic where data was collected on lifestyle, smoking status, blood pressure, blood count, and lipid levels. Treatments were offered to individuals at risk for hypertension and/or dyslipidemia based on risk factors, including age and gender. Patients with other illnesses or opium addiction were excluded from the trial. Of the 1733 individuals, 872 patients without hypertension, CVD, or dyslipidemia and who were not taking anti-platelet drugs or medications for hypertension or dyslipidemia were included in the two-month run-in phase of the trial. Due to non-compliance and health factors, only 475 participants were ultimately randomized to receive either the polypill, which contained a fixed-dose combination of aspirin 81 mg, enalapril 2.5 mg, atorvastatin 20 mg, and hydrochlorothiazide 12.5 mg, or placebo once daily. Due to concern of hypotension, the enalapril was maintained at a lower-than-therapeutic dose. The primary outcomes were changes in blood pressure and LDL-cholesterol and any adverse reactions. Secondary outcomes were changes in total and HDL-cholesterol, triglycerides, and fasting glucose.

Three hundred and forty-eight patients finished the 12-month follow-up patients, with more patients finishing in the control group than in the intervention group (78.2% vs. 68.5%; p=0.016). At the 12-month follow-up, the intervention group had lower systolic blood pressure (treatment difference 4.5 mmHg; p<0.001), lower diastolic blood pressure (treatment difference 1.6 mmHg; p<0.032), lower LDL-cholesterol (treatment difference 0.46 mmol/L; p<0.001), and lower total cholesterol (treatment difference 0.63 mmol/L; p<0.001) compared to the placebo group. Triglycerides were 0.16 mmol/L (11.3%) lower (p<0.005), HDL cholesterol was 0.01 mmol/L (0.9%) higher (p=0.575), and fasting glucose was 0.17 mmol/L (3.3%) lower (p=0.008) in the intervention group. Compliance, as determined by inquiry and pill count, was 89% in both groups. Few adverse effects were reported, but more people discontinued the polypill than the placebo (78.2% vs. 68.5%). The authors concluded that the polypill was effective in modifying risk factors associated with CVD. Differences in gender and blood pressure between groups at baseline may have affected the outcome differences found in this study.

SUMMARY: The use of aspirin, enalapril, atorvastatin, and hydrochlorothiazide in the format of a polypill lowered blood pressure, LDL cholesterol, triglycerides, and total cholesterol and increased HDL cholesterol in relatively healthy individuals.


By Derk Penrod, Pharm.D. Candidate
Major depressive disorder (MDD) can be especially difficult to treat, and up to 50% of patients remain symptomatic despite therapy with first-line medications, selective serotonin reuptake inhibitors (SSRIs). When SSRIs fail to adequately treat depression, a second agent such as a serotonin and norepinephrine reuptake inhibitor (SNRI) or a dopamine agonist is typically added. Current guidelines only recommend the use of herbal or dietary supplements for mono-therapy in mild to moderate depression due to the lack of evidence supporting their safety and tolerability as adjunctive treatment and their unknown efficacy in severe depression.

The dietary supplement S-adenosyl methionine (SAMe) is also produced by the body and is involved in the formation of neurotransmitters (e.g., serotonin, dopamine, norepinephrine), amino acids, DNA, RNA, and lipids. Because serotonergic and dopaminergic activity is increased with SAMe, its combination with other antidepressants as adjunctive treatment in MDD has been assessed in relatively recent clinical trials.

An open-label pilot study evaluated the efficacy, safety, and tolerability of oral SAMe as adjunctive therapy to SSRI or SNRI in resistant MDD. In the six-week trial, 30 patients with MDD who were resistant to treatment with an SSRI (fluoxetine/paroxetine/citalopram ≥20mg daily, escitalopram ≥10mg daily, sertraline ≥50mg daily) or an SNRI (venlafaxine ≥75mg daily, duloxetine ≥60mg daily) for at least six weeks prior to the beginning of the study, and all had HAM-D scores of ≥16 at baseline. Patients were randomly assigned to receive either 400mg SAMe twice daily for two weeks, then 800mg SAMe twice daily for four weeks or a placebo for six weeks, both in addition to their SSRI/SNRI treatment. The primary endpoint was the responder rate difference between groups, and the secondary endpoints included the proportion of patients who reached remission status at six weeks. Responders were defined as those with a ≥50% reduction in HAM-D scores or a final score of ≤7, and remission status was achieved with a final HAM-D score of ≤7. The difference in HAM-D scores between groups when compared to baseline were not significant at six weeks (p=0.1). However, there were more responders and patients in remission in the SAMe group (47% and 37%, respectively) versus the placebo group (18% and 12%, respectively; p=0.02). The authors shared the same conclusions as those in the previous trial. Limitations of the study included a small sample size and a short duration. Additionally, the trial may not have found significant results because it was underpowered.

There were no serious adverse events reported in either study. Adverse events such as gastrointestinal upset, diarrhea/gas, decreased appetite, headaches, anxiety/irritability, fatigue/sedation, and sleep disturbances were similar between both studies. Both studies showed potential efficacy with the use of SAMe as adjunctive therapy with SSRIs in refractory MDD. Both studies also indicated that SAMe was relatively well-tolerated and safe. However, follow-up with further studies with larger sample sizes is needed in order to confirm these findings.

By Jon Knecht, Pharm.D. Candidate

REFERENCES:
There is a direct positive correlation between serum uric acid levels and gout. Increased serum uric acid is caused by either overproduction and/or underexcretion of uric acid, and xanthine oxidase inhibitors (e.g., allopurinol), which decrease uric acid synthesis, are effective for gout attack prophylaxis in both cases. In September 2010, the FDA approved Krystexxa® (pegloticase) for the treatment of chronic, refractory gout. Pegloticase lowers serum uric acid concentration by catalyzing the oxidation of uric acid into allantoin, a purine metabolite that is inert, water soluble, and readily eliminated.

A phase II, randomized, open-label, parallel-group trial of multiple doses and regimens of pegloticase was conducted to assess the efficacy and safety in patients with treatment-failure gout. Forty-one patients ≥18 years of age with serum uric acid levels ≥8 mg/dL, established and symptomatic gout, and a history of unsuccessful treatment with or contraindication to urate-lowering treatment were included in the trial. Following a one-week urate-lowering treatment washout period, patients were randomized to IV infusions of pegloticase, either 4 mg or 8 mg every two weeks for a total of six doses or 8 mg or 12 mg every four weeks for a total of three doses. The primary efficacy endpoint was the percentage of treatment responders, defined as patients with plasma urate levels ≤6 mg/dL for a duration of 80% or more of the study period. The secondary efficacy endpoints included the percentage of time without hyperuricemia, mean plasma urate levels, and the relative reduction of the plasma urate level from baseline. Safety and tolerability endpoints were also evaluated. The primary endpoint was met within six hours after the initial dose in all dosage groups and was sustained throughout the treatment period in both 8 mg groups and the 12 mg group. The mean plasma urate levels for each treatment group were 4.12 ± 2.02 mg/dL in the 4 mg group, 1.42 ± 2.06 mg/dL in the 8 mg every-two-weeks group, 3.21 ± 2.26 mg/dL in the 8 mg every-four-weeks group, and 3.09 ± 2.46 mg/dL in the 12 mg group, with reduction from baseline values of 38 ± 31%, 86 ± 18%, 58 ± 36%, and 67 ± 22%, respectively. The mean total percentage of time without hyperuricemia among patients in each treatment group was >75%. Overall, 93% of patients reported adverse events, with a similar incidence across all treatment groups. The most common events were nephrolithiasis and arthralgias, with infusion-related adverse reactions accounting for 12.7% of all events. The majority of adverse events (60%) were considered by the investigators to be unrelated to the study treatment, and 93% were considered mild or moderate in severity. Eighty-eight percent of patients reported one or more gout flares during the study, but this was a well known complication of urate-lowering treatment initiation. The authors concluded that pegloticase resulted in rapid and sustained reduction of plasma urate levels in patients with gout with the 8 mg every-two-weeks group having the highest proportion of responders and the highest percentage of time without hyperuricemia; however, the differences between treatment groups was not significant. Potential limitations of this trial included the small sample size, open-label design, and short duration of treatment.

Adverse reactions commonly seen with pegloticase include chest pain (6%), constipation (6%), nausea (12%), vomiting (5%), acute gout flare (74-81% within the first three months of therapy), and nasopharyngitis (7%). Serious adverse reactions seen with pegloticase include anaphylaxis (4.6-6.5%) and infusion complications (26-41%). Pegloticase 8 mg IV every two weeks is approved for refractory gout prophylaxis, but the optimal duration of therapy has not been established.

Pegloticase has a novel mechanism of action in gout therapy by converting urate to allantoin, which is more soluble and easily excreted creating a treatment option for patients who have contraindication to or who have failed treatment with xanthine oxidase inhibitors.

By Kimberly Swanson, Pharm.D. Candidate

(references on page 4)
Levonorgestrel (LNG) is the most common emergency contraception (EC) currently used. LNG has a pregnancy rate of 1.5–2.6% if taken within 72 hours of unprotected intercourse (UPI). LNG is effective at blocking the luteinizing hormone (LH) surge that precedes follicular rupture, but once the LH surge has triggered the ovulatory process, LNG is no longer able to prevent the release of the oocyte. Ulipristal acetate (UPA) is a selective progesterone receptor modulator that prevents follicular rupture after the LH surge has begun, as demonstrated by a double-blind, placebo-controlled, randomized, cross-over study of the effect of 30 mg of ulipristal on the leading follicle immediately before ovulation.

Thirty-four female patients with non-hormonal intrauterine devices or tubal ligations to prevent pregnancy completed the UPA study. Patients underwent daily ultrasound monitoring to determine when the lead follicle reached >18 mm in size, at which time they were given either UPA 30 mg or an identical looking placebo. Daily ultrasounds and hormone assays were then performed for five subsequent days to determine follicle status. After a 2-cycle wash out period, patients were given the other treatment. The primary endpoint was the delayed rupture of the lead follicle by more than five days. In the placebo cycles, all 34 follicles had ruptured within 5 days. In the UPA treatment group, 20 out of 34 patients (58.8%, 95% CI 40.7 to 75.4%) had no follicle rupture within 5 days. However, the LH status at the time of treatment affected the results of UPA treatment. Taking UPA before the LH surge onset (which occurred in 8 women) resulted in no follicle rupture within 5 days in any of the women. Treatment after the LH surge but before the LH peak caused no follicle rupture within 5 days in eleven of 14 women (78.6%, 95% CI 49 to 95%). Treatment after the LH peak resulted in no follicle rupture within 5 days in only 1 of 12 women (8.3%, 95% CI 0.2 to 35.8%). The authors concluded that UPA may be an effective EC if used after LNG is no longer able to inhibit ovulation. This study had a small patient population, and because it did not examine patient-oriented outcomes such as morbidity and mortality, its clinical utility is somewhat limited.

SUMMARY: Unlike LNG, which is no longer able to inhibit ovulation once the LH surge has begun, UPA delayed follicular rupture up to five days after the LH surge had initiated.

By Michael Harrington, Pharm.D. Candidate

Krystexxa® (from page 3)

REFERENCES:

LITERATURE HIGHLIGHT: Ulipristal Acetate and Follicular Rupture
Patients with isolated superficial-vein thrombosis are at risk for subsequent venous thromboembolic complications such as deep-vein thrombosis (DVT) or pulmonary embolism (PE). Current recommendations for these patients suggest either no treatment or treatment with anti-inflammatory agents, anticoagulants, or surgery to prevent complications. A multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of fondaparinux in reducing symptomatic venous thromboembolic complications or death from any cause in patients with acute, isolated, superficial-vein thrombosis of the legs.

Three thousand and two eligible patients, 18 years of age or older, were randomized to receive either fondaparinux 2.5 mg or placebo subcutaneously once daily for 45 days. The primary efficacy endpoint was the composite of death from any cause, documented symptomatic PE, symptomatic thrombotic extension to the saphenofemoral junction, or symptomatic recurrence of superficial-vein thrombosis up to day 47. Secondary efficacy endpoints were the composite primary efficacy outcome up to day 77 and each component of the primary endpoints, the composite of symptomatic PE or DVT, and surgery for superficial-vein thrombosis up to day 47 and day 77. In an intent-to-treat analysis, the primary efficacy endpoint occurred in 13 of 1502 (0.9%) fondaparinux patients compared to 88 of 1500 (5.9%) patients in the placebo group (RR 0.15, 95% CI 0.08 to 0.26; p<0.001). The incidence of each component of the primary efficacy endpoint was significantly reduced in the fondaparinux group compared to placebo, except for incidence of death, which did not differ significantly between groups. The risk of composite DVT or PE at day 77 was reduced with fondaparinux (RR 0.18, 95% CI 0.06 to 0.53; p<0.001). Three of 1502 patients (0.2%) experienced a thrombotic event in the fondaparinux group by day 47 compared to 20 of 1500 patients (1.3%) in the placebo group (RR 0.15, 95% 0.05 to 0.50; p<0.001). More patients in the placebo group compared to the fondaparinux group underwent surgery for superficial-vein thrombosis by day 77 (2.5% vs. 0.5%; RR 0.25, 95% CI 0.14 to 0.43). The rates of major, relevant nonmajor, minor, and total bleeding and arterial thromboembolic complications did not differ significantly between the two groups, and results were maintained at day 77. The authors concluded the patients in the study were representative of those encountered in regular practice and that fondaparinux may be an effective treatment in preventing thromboembolic complications following superficial-vein thrombosis in the legs. A complete ultrasound exam was performed in every patient with a suspected superficial-vein thrombosis to confirm thrombosis and rule out DVT. This process may be too costly to routinely implement in clinical practice and limits the clinical applicability of the study.

SUMMARY: Fondaparinux 2.5 mg once daily for 45 days decreased the occurrence of thrombotic events and death following superficial-vein thrombosis of the legs.


By Kimberly Swanson, Pharm.D. Candidate