A summary of current literature of interest to pharmacists.
Alan Hopefil, Pharm.D., Amerinet Senior Clinical Manager

Amerinet Clinical Publications

The December 2012 issue of the Amerinet PharmAdvisor contains a review of “Tofacitinib (Xeljanz™), The First Oral Janus Kinase Inhibitor”.

The March 2013 issue of Amerinet Clinical News contains summaries of articles on:
- Consequences of Discontinuing Rivaroxaban in Patients with Atrial Fibrillation
- Rivaroxaban for Thromboprophylaxis in Medical Patients
- Usefulness of Daptomycin for Patients with Staphylococcus aureus Bacteremia
- Dosing and Clinical Outcomes from Converting from Insulin Glargine to Insulin Detemir
- A Potential Alternative Drug to Linezolid

Institute for Safe Medical Practices (ISMP)

The February 21, 2013 issue of ISMP is available. Your complimentary subscription is an educational service of Amerinet.

Clinical News

Many patients with chronic idiopathic urticaria do not have a response to therapy with H1-antihistamines. A phase 3, randomized, double-blind study was done to evaluate the efficacy and safety of omalizumab (Xolair™) in patients with moderate-to-severe chronic idiopathic urticaria who remained symptomatic despite H1-antihistamine therapy. There were 323 patients who were randomized to receive 3 subcutaneous injections of omalizumab at doses of 75 mg, 150 mg, or 300 mg or placebo spaced 4 weeks apart. At week 12, the mean change from baseline in the weekly itch severity score was similar in the placebo and 75 mg omalizumab groups, but was significantly improved in the 150 mg [P=0.001] and 300 mg [P<0.001] omalizumab groups. The frequency of serious adverse events was low, although the rate was higher in the 300 mg group (6%) than in the placebo group (3%) or in either the 75 mg or 150 mg groups. Omalizumab diminished the clinical symptoms and signs of chronic idiopathic urticaria in patients who are symptomatic despite use of approved doses of H1-antihistamines.

A historical cohort of over 600,000 pregnancies in Denmark was used to assess the risk of adverse fetal outcomes associated with ondansetron administered during pregnancy. The receipt of ondansetron was not associated with a significantly increased risk of spontaneous abortion which occurred in 1.1% of exposed women and 3.7% of unexposed women during gestational weeks 7 to 12, and in 1.0% and 2.1% during weeks 13 to 22. Ondansetron also conferred no significantly increased risk of still birth, any major birth defect, or preterm delivery. Ondansetron taken during pregnancy was not associated with a significantly increased risk of adverse fetal outcomes.

Previous studies have raised the possibility that incretin-based therapies, including glucagon-like peptide-1 (GLP-1) mimetics and dipeptidyl peptidase-4 (DPP-4) inhibitors may increase the risk of acute pancreatitis. A large administrative database was used to test whether exenatide and sitagliptin were associated with an increase risk of acute pancreatitis. In adults with type 2 diabetes, aged 18 to 64 years, there were 1264 hospitalized cases of acute pancreatitis using these agents who were matched with control subjects. Cases of acute pancreatitis were more likely than controls to have hypertriglyceridemia, use alcohol, have gallstones, abuse tobacco, be obese, have biliary or pancreatic cancer, or any cancer. After adjusting for confounders, the current use of exenatide or sitagliptin within 30 days had an adjusted odds ratio of 2.24, and use within < 2 years an OR= 2.01 indicating a significantly increased odds of acute pancreatitis compared to nonusers.

A Markov model with a lifetime horizon and two states, alive or dead, was created to quantify the incremental cost-effectiveness ratios of ACE inhibitors, β-blockers, and aldosterone antagonist therapies for patients with heart failure with reduced ejection fraction. The greatest gains in quality-adjusted life-years (QALY) occurred when all 3 classes of drug were provided to patients. The incremental cost-effectiveness ratio of ACEI+BB+aldA versus ACEI+BB and ACEI+BB versus ACEI alone was <$1500/QALY. The medical treatment of heart failure is highly cost-effective and may result in overall cost savings.

In the HPS2-THRIVE study, 25,673 patients were randomized to extended-release niacin/laropiprant (2gm/40mg) or placebo in addition to simvastatin 40 mg daily to assess the effects in patients at high risk of vascular events. Patients were followed for a median of 3.9 years. By the end of the study, 25% of participants receiving ERN/LRPT vs. 17% allocated to placebo had stopped their study drug. The most common medical reasons for stopping ERN/LRPT were related to skin, gastrointestinal, diabetes, and musculoskeletal side effects. When added to statin therapy ERN/LRPT increased the risk of definite myopathy from 0.04%/year to 0.16%/year, risk ratio = 4.4. Any myopathy was more common among participants in China, 0.66%/year vs. 0.04%/year in Europeans. Merck has recently suspended clinical development of ERN/LRPT.
A meta-analysis of depression outcomes was done on individual patient data of 2470 patients with depression from 16 datasets comparing low-intensity interventions with usual care. Low-intensity interventions included guided self help by means of written materials and limited professional support, and internet delivered interventions. Although patients were referred for low intensity interventions, many had moderate-to-severe depression at baseline. There was a significant interaction between baseline severity and treatment effect suggesting that patients who were more severely depressed at baseline demonstrated larger treatment effects than those who are less severely depressed. This suggests that patient with more severe depression at baseline show at least as much clinical benefit from low-intensity interventions as less severely depressed patients and could be offered these interventions as part of a stepped care model for depression treatment.

The 5-year results of the SYNTAX trial, which compared CABG with PCI in patients with left main or 3-vessel coronary artery disease has been published. There were 1800 patients randomly assigned to either CABG (n=897) or PCI. After 5-years of follow-up, major adverse cardiac and cerebrovascular events were 26.9% in the CABG group and 37.3% in the PCI group, [P<0.0001]. Estimates of MI, 3.8% in the CABG group vs. 9.7% in the PCI group, [P<0.0001] and repeat revascularizations, 13.7% vs. 25.9%, [P<0.0001] were significantly increased in the PCI group compared to the CABG group. CABG should remain the standard of care for patients with complex CAD lesions. For patients with less complex disease, or left main disease, PCI is an acceptable alternative.

Lithium has neuroprotective effects and a small study showed a significant effect on survival in patients with amyotrophic lateral sclerosis (ALS). In a randomized, double-blind, placebo-controlled trial, 214 patients with ALS, all of whom were taking riluzole, received either placebo(n=107) or lithium (n=107) for 18 months. Fifty-nine percent of patients in the placebo group and 50% in the lithium group were alive at 18 months. The survival functions did not differ significantly between groups. Fifty-two percent of patients in the placebo group and 57% of patients in the lithium group had at least one serious adverse event. There appears to be no benefit with lithium therapy on survival in patients with ALS.

**Guideline and Disease Review Updates**

The American Academy of Pediatrics and the American Academy of Family Physicians have released their updated clinical practice guidelines for the Diagnosis and Management of Acute Otitis Media (AOM). It provides recommendations to primary care clinicians for the management of children from 6 months through 12 years of age who have uncomplicated AOM. The guideline addresses pain management, initial observation versus antibiotic treatment, appropriate choices of antimicrobial agents, and preventative measures. It also addresses recurrent AOM, which was not included in the 2004 guidelines.

The United States Preventative Services Task Force has released recommendations on vitamin D and calcium supplementation to prevent fractures in adults. These recommendations apply to noninstitutionalized or community-dwelling asymptomatic adults without a history of fractures. The USPSTF concludes that current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men. They also conclude that current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 400 IU of vitamin D and greater than 1000 mg of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women.

The USPSTF recommends against daily supplementation with 400 IU of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women.

A review of the use of non-heparin anticoagulants for patients with heparin-induced thrombocytopenia (HIT) has been published. It reviews the pathophysiology of HIT, the clinical use, and clinical evidence of alternative anticoagulant agents, such as direct thrombin inhibitors, hirudins, and fondaparinux.

**From the FDA and CDC**

The FDA has approved ado-trastuzumab emtansine (Kadcyla™) for use as a single agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane. The approval is based on a randomized, open-label study of 991 patients with HER2-positive metastatic breast cancer. The patients in the study received either ado-trastuzumab emtansine intravenously on day 1 and every 21 days or lapatinib 1250 mg/day for 21 days plus capecitabine 1000 mg/M² twice daily for 14 days. The overall survival was 30.9 months in the ado-trastuzumab emtansine group compared with 25.1 months in the lapatinib/capecitabine group, [P=0.0006].

**Vaccine and Influenza Update**

Dynavax Technologies Corporation has announced that it has received a Complete Response Letter from the FDA regarding its BLA for Heplisav™. Heplisav is an investigational adult hepatitis B vaccine that combines hepatitis B surface antigen with a proprietary Toll-like Receptor
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9 agonist to enhance the immune response. The FDA has specified that the vaccine cannot be approved without further evaluation of safety in the broad age range of 18 to 70 years. The FDA is also concerned that the novel adjuvants may cause rare autoimmune events. FDA has also requested additional data on manufacturing controls and facilities related to the assurance of the quality of the commercial product.

A retrospective analysis was done to evaluate the risk of narcolepsy in children and adolescents targeted for vaccination with AS03 adjuvanted pandemic influenza A/H1N1 2009 vaccine (Pandemrix™). The case notes for 245 children and young people were reviewed showing that 75 had narcolepsy. Eleven had been vaccinated before onset of narcolepsy and seven within six months. The odds ratio was 14.4 for vaccination at any time before onset and 16.2 for vaccination within 6 months before onset. The attributable risk was estimated to be between 1 in 57,500 and 1 in 52,000 doses. The increased risk of narcolepsy after vaccination with ASO3 adjuvanted pandemic A/H1N1 2009 vaccine indicates a causal association, consistent with findings from Finland. Note that the FDA has not approved this adjuvant for use in vaccines available in the U.S.

Healthcare Industry News

Takeda Pharmaceuticals/Affymax have decided to voluntarily recall all lots of peginesatide (Omontys™) to the user level as a result of new postmarketing reports regarding serious hypersensitivity reactions, including anaphylaxis. The companies have also issued a letter to healthcare professionals indicating that no new or existing patients should receive Omontys. To date, fatal reactions have been reported in approximately 0.02% of patients following the first dose of intravenous administration. The reported hypersensitivity reactions have occurred within 30 minutes of administration. Customers will be provided with instructions on how to return the product to the manufacturer for a refund.

Repros Therapeutics has provided a clinical update of its clomifene (Androxal™) phase 3 program following receipt of written guidance from the FDA. The FDA has informed Repros to proceed with the analysis of ZA-301 study as previously planned. Additionally, the FDA accepted Repros’ plan regarding study ZA-302 to enroll additional patients.

Eighty percent of all antibiotic use in the United States is used in food-animals, many of whom are perfectly healthy. This may be one of the factors responsible for the increase in antibiotic resistance. Congress has introduced the Delivering Antimicrobial Transparency in Animals Act, which would require pharmaceutical manufacturers to obtain and provide better information to the FDA on how their drugs are used in food-producing animals. The bill would also require producers of poultry, livestock, and swine to report data on the use of medications given to their livestock.

Continuing Education

Amerinet is pleased to announce that links have been added in Member Resources to take you directly to ACPE accredited continuing education programs that are available through Inquisit. By clicking on the appropriate link you are taken to a list of upcoming live CE programs or a list of “Learning on Demand” programs. You can get to the CE program indexes by signing into Member Resources, selecting pharmacy under Contracting Tools, then clicking on Information and Education.

Amerinet Information Exchange

To pose a question on pharmacy issues such as patient services, department policies, or JCAHO surveys to members of the Amerinet e-mail community, please send your question to: alan.hopefl@amerinet-gpo.com. When composing your question, please be specific regarding the type of information that you would like. Amerinet reserves the right to determine the appropriateness of topics for broadcast and will clarify any issues with the requester, if necessary prior to distribution of the request. Drug bartering requests will not be a part of the service. If a request is not appropriate for distribution, an e-mail explaining why it is not appropriate is sent back to the author. Requests will be broadcast to the Amerinet e-mail community within 2 business days of acceptance. The e-mail address of the author will be included in each information request e-mail. Subscribers will be asked to reply directly to the author if they have information to share. We hope this service is beneficial for you. Please contact me at the above email address should you have any questions or comments. Members who are not currently enrolled in PEMS can do so by sending their contact information to Alan Hopell at alan.hopefl@amerinet-gpo.com. Once enrolled you will start receiving the e-mail newsletters and you may send a request for information to the address listed above.
Amerinet
Reducing healthcare costs. Improving healthcare quality.

As a leading national group purchasing organization, Amerinet strategically partners with healthcare providers to reduce costs and improve quality.

Through Amerinet’s total spend management solutions and operational performance improvement tools and services, we assist providers in reducing costs, improving efficiencies and creating new revenue streams.

Supported by a team of clinical, data and supply chain experts, Amerinet offers a comprehensive and competitive portfolio of product and service contracts designed to address members’ specific needs.

Amerinet, Inc.
2060 Craigshire Road, St. Louis, MO 63146
P 877-711-5600
www.amerinet-gpo.com