Safety Update: Erythropoiesis-Stimulating Agents - Epogen® (epoetin alfa), Procrit® (epoetin alfa) and Aranesp® (darbepoetin)

Erythropoiesis stimulating-agents (ESAs) are blood modifying agents that work by stimulating red blood cell (RBC) production and include epoetin alfa (Epogen®, Procrit®) and darbepoetin (Aranesp®). These agents are most commonly used to treat anemia associated with chronic kidney disease (CKD), for patients both on and off dialysis, as well as to treat anemia in cancer patients receiving chemotherapy. The goal of ESA treatment is to maintain hemoglobin (Hb) levels within a therapeutic range and decrease the need for RBC transfusions. However, controversy has surrounded the use of ESAs in patients with CKD due to recent randomized controlled clinical trials which re-evaluated the target Hb levels in pre-dialysis patients with CKD.

In November 2006, 2 studies were published indicating that patients treated with ESAs, dosed at a target Hb concentration of > 12 g/dL, experienced an increased risk for death, cardiovascular events (including more hypertension and congestive heart failure), and more rapid progression to hemodialysis compared to patients targeted to lower Hb levels. The Correction of Hemoglobin Outcomes in Renal Insufficiency (CHOIR) study and the Cardiovascular Risk Reduction by Early Anemia Treatment with epoetin beta (CREATE) study, both published in the New England Journal of Medicine, evaluated patients in early stages of CKD. The results of these studies prompted the Food and Drug Administration (FDA) to require the manufacturers to change product labeling and include a black box warning. This update will focus on additional published information regarding the safety of ESAs, including revisions to product labeling and implications for patient care.

Literature Update: Findings of a meta-analysis

Shortly after the results of the CHOIR and CREATE studies were revealed, Phrommintikul and colleagues published a meta-analysis to determine whether targeting various Hb concentrations when treating patients with anemia secondary to CKD with ESAs is associated with all-cause mortality and cardiovascular events. In this meta-analysis, 9 randomized controlled clinical trials that enrolled 5143 patients were assessed. In each of these studies, at least 100 patients were randomized to treatment with recombinant human erythropoietin, and the minimum treatment duration was 12 weeks. Four of the studies included patients that were on dialysis. Epoetin alfa was administered in 8 studies, and epoetin beta, which is not FDA-approved, was administered in 1 study.

The target Hb concentrations in the high Hb groups ranged from 12 to 16 g/dL; the range in the low groups was 9 to 10.5 g/dL. The risk of all-cause mortality was significantly increased in the high Hb target groups compared to the lower Hb target groups (risk ratio = 1.17; 95% confidence interval (CI) 1.1 to 1.35, p = 0.031). Of the 9 studies included, 7 reported data on myocardial infarction (MI); there was no difference found between the 2 groups (risk ratio = 0.98; 95% CI 0.73 to 1.81; p = 0.067). Two additional endpoints included poorly controlled hypertension and arteriovenous (AV) access thrombosis. Both endpoints were significantly greater in the high Hb groups compared to the low Hb groups (risk ratio = 1.27; 95% CI 1.08 to 1.50; p = 0.004) and (risk ratio = 1.34; 95% CI 1.16 to 1.54; p = .0001), respectively.

Increased Risk with ESAs in Cancer Patients

Cancer patients receiving radiotherapy

In December 2006, Amgen, the manufacturer of Aranesp (darbepoetin) informed the FDA of the interim results of the Danish Head and Neck Cancer Study Group trial (DAHANCA 10). This open-label, randomized trial compared radiation therapy alone to radiation therapy plus darbepoetin in
Cancer patients not receiving chemotherapy

The FDA was notified in January 2007 of the results of a 989 patient, multicenter, double-blind, randomized, placebo-controlled study of darbepoetin in anemic cancer patients not receiving chemotherapy. The target Hb in the treatment group was 12 g/dL. The results of the study indicated that darbepoetin did not reduce RBC transfusions and was associated with increased mortality in patients receiving treatment compared to those receiving placebo (hazard ratio = 1.25; 95% CI 1.04 to 1.51).

The results of another trial in anemic patients with non-small cell lung cancer not receiving chemotherapy found that treatment with epoetin did not improve quality of life. In this double-blind, placebo-controlled study the epoetin dosage was titrated to maintain Hb levels of 12 to 14 g/dL. Although the investigators planned to enroll 300 patients, the study enrolled only 70 patients and was stopped early due to a higher incidence in mortality observed in patients treated with epoetin. Median time to death in those treated with epoetin was 68 days, significantly shorter than the median time to death of 131 days in those treated with placebo (p = .04). In addition, treatment with epoetin did not significantly reduce the need for RBC transfusions or improve quality of life.

Increased Risk with ESAs in Patients Undergoing Surgery

The preliminary results of a multicenter, randomized, open-label, non-inferiority study in 681 patients that compared epoetin to “standard of care” in adult patients undergoing elective spinal surgery were recently reported to the FDA. Epoetin was administered according to the prescribing information for pretreatment Hb values >10 and < 13 g/dL. The frequency of deep venous thrombosis (DVT) in patients treated with epoetin was 4.7% (16 patients), which was more than twice that of patients who received usual standard of care.

Changes in the Prescribing Information for ESAs

As a result of the studies reviewed above, the FDA along with the manufacturers of the ESAs has recently updated the prescribing information for these agents. A new black box warning provides the following information:

- Avoid serious cardiovascular and arterial and venous thromboembolic events by using the lowest dose of [Aranesp /Epogen/Procrit] that will gradually raise the Hb concentration to the lowest level sufficient to avoid the need for blood transfusion.
- Aranesp/Epogen/Procrit increase the risk for death and for serious cardiovascular events when dosed to achieve a target Hb of greater than 12 g/dL.
- ESAs increase the risk of death when administered to target a Hb of 12 g/dL in patients with active malignant disease who are not receiving chemotherapy or radiation. ESAs are not indicated for this population.
- Patients treated before surgery with epoetin to reduce allogeneic RBC transfusions had a higher incidence of DVT. Aranesp is not approved for this indication.

Additional warnings about increased mortality, cardiovascular events, tumor progression and uncontrolled hypertension with ESAs are summarized below:

- Increased mortality and cardiovascular events – the warnings now describe the results of new studies showing an increased incidence of thrombotic events in patients with CKD, cancer patients on chemotherapy, and surgical candidates.
- Potential for tumor growth progression – a subsection in the warnings describes new data and emphasizes the evidence for increased rate of tumor progression.
- Hypertension – this subsection advises against the use of ESAs in patients with uncontrolled hypertension, and describes the risks to and guidance for managing controlled hypertensive patients.

Guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) and National Comprehensive Cancer Network (NCCN)

The National Kidney Foundation in 2006 recommended a hemoglobin range of 11 to 13 g/dL for patients with anemia of CKD. However, due to this new safety information regarding ESAs, the National Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) will recommend that the selected Hb target should “generally be in the range of 11 to 12 g/dL”. The National Comprehensive Cancer Network (NCCN) has recently updated their guidelines; this group currently recommends target Hb ranges of 11 to 12 g/dL for anemic cancer patients receiving cancer-related therapy (chemotherapy or radiation).

Recommendations for Patient Care

Physicians and other healthcare professionals should consider the following when using ESAs:

For all patients:

- Use the lowest dose possible to gradually increase the Hb concentration to avoid the need for transfusion.
- Measure Hb twice a week for 2 to 6 weeks after any dosage adjustment to ensure that Hb has stabilized in response to the dose change.
- Withhold the dose of the ESA if the Hb increase
exceeds 12 g/dL or rises by 1 g/dL in any 2 week period.

For cancer patients:
- Use of an ESA in anemic cancer patients who are not on chemotherapy offers no benefit and may shorten the time to death.
- ESAs are not FDA-approved to treat anemia in cancer patients not receiving chemotherapy.
- There is a potential risk of shortening the time to tumor progression or disease-free survival with ESAs.
- ESAs are administered only to avoid RBC transfusions in cancer patients. ESAs do not improve the outcome of cancer treatment and do not alleviate fatigue or increase energy.

For chronic renal failure (CRF) patients:
- Measure Hb twice a week after initiating treatment until Hb has stabilized.

For cancer patients and zidovudine-treated HIV patients:
- Measure Hb once a week after initiating treatment until Hb has stabilized.

For patients with a history of cardiovascular disease or hypertension:
- Closely monitor and control blood pressure

Patient Counseling Information
- The goal of treatment with ESAs is to increase the number of RBCs to avoid blood transfusions.
- ESAs require at least 2 to 6 weeks of treatment before there is an increase in the number of RBCs.
- The effects of treatment with an ESA can be harmful in certain circumstances.
- Patients should keep appointments for blood tests so they can be adequately monitored.
- Patients need to monitor blood pressure every day (if appropriate) and call their health care provider if there are any changes outside of the range established for the patient.

Patients should contact a health care provider if they experience any of the following symptoms:
- Pain and/or swelling in the legs
- Worsening in shortness of breath
- Increases in blood pressure
- Dizziness or loss of consciousness
- Extreme tiredness
- Blood clots in hemodialysis vascular access ports

CDC Recommendations for the Use of Gardasil

Introduction
Human papillomavirus (HPV) is the most common sexually transmitted infection, affecting approximately 6.2 million Americans every year. These infections usually occur in the adolescent and young adult population between the ages of 15 and 24. Additionally, about 80% of women who have been sexually active in the United States have acquired an HPV infection by the age of 50. Most often HPV is an asymptomatic, self-limited infection which lasts a median of 8 months; however, HPV may also lead to genital warts and cervical or other anogenital cancers.

There are 40 types of HPV which infect the human mucosa. The majority of these are considered low risk and 90% of genital warts are due to infection with low risk HPV types 6 and 11. Ten HPV types are categorized as high risk types due to the presence of oncogenes as a part of their DNA. Infection with one of these 10 types may progress to cancer. Two high risk types are associated with a majority of the cervical cancer seen in the United States. Type 16 is responsible for 50% of cervical cancer cases, whereas type 18 is responsible for an estimated 10 to 12% of cases.

Gardasil® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]
It is estimated that 11,000 women will be diagnosed with cervical cancer, and 3,700 will die this year. Since 1950, the incidence of cervical cancer has decreased by 75% due to cancer screenings and regular pap smears. In June 2006, the Food and Drug Administration (FDA) approved a vaccine that could further decrease the rate of cervical cancer. Gardasil is a quadrivalent vaccine indicated for girls and women 9 to 26 years of age for the prevention of cervical cancer, genital warts, and precancerous lesions caused by HPV types 6, 11, 16, and 18. It is administered as a series of 3 intramuscular injections, with the second and third vaccinations given 2 and 6 months after the initial immunization, respectively. The Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) reviewed the clinical data for the Gardasil vaccine and published recommendations which are summarized below.

Recommendations
- The Gardasil series should be administered to girls between the ages of 11 and 12 years as a part of their regular vaccinations.
- Adolescents and women 13 to 26 years of age should be vaccinated if they have not been already.
- Gardasil should not be administered during pregnancy; however, it may be administered to lactating women.
- Although males can be infected with HPV, the vaccine is not approved for use in males at this time; however, safety and efficacy trials are being conducted.

Clinical data show that Gardasil provides the greatest protection against HPV when the entire series is given prior to the onset of sexual intercourse; therefore, the ACIP recommends that the best time to vaccinate is best at age 11 and 12 years. However, adolescents and women who are already sexually active or have been previously infected with HPV, should still receive the vaccine because it is unlikely that many individuals would have been infected with all 4 types of HPV.

Gardasil will not treat a current HPV infection and the ACIP stresses that routine cervical cancer screenings and safe sex practices are necessary to prevent HPV types not covered by the vaccine. Though long term studies are still being conducted to determine the length of protection from vaccination, current
data shows that the vaccine is effective for at least 5 years.

Studies confirmed that the most common adverse events associated with the vaccine were pain and redness at the site of injection. Other adverse reactions included dizziness, fever, and nausea. The CDC and FDA are continuing to collect information regarding the safety of Gardasil. Health care providers can assist by going to the following website to report relevant adverse events: http://vaers.hhs.gov.

Cervarix™ [Human Papillomavirus Bivalent (Types 16, and 18) Vaccine]
Early clinical evidence indicates that an investigational vaccine, expected to be available by the end of 2007, offers protection against HPV types 16 and 18. Studies have shown that Cervarix is 100% effective in the prevention of infection with these types of HPV. Cervarix also appears to elicit a better immune response in girls between 10 and 14 years of age when compared to females age 15 to 25 years.

Controversy
Though very often government agencies and states accept the guidance of ACIP, not all groups believe that the recommendations should be implemented. Some argue that vaccinating girls against a disease that is only transmitted via sexual contact should be a choice. Some individuals fear that vaccinating adolescent females will encourage sexual activity and give the impression that the vaccine will decrease the risk of contracting a sexually transmitted disease (STD), despite data that indicates the education of teens on the correct use of condoms has not increased sexual activity. In early July, it was reported that the only state to require HPV vaccination for school enrollment is Virginia. There are 16 other states in which legislation is pending requiring the vaccine, funding vaccination, or education of constituents about the HPV vaccine. Illinois is not one of these states.

Summary
Human papillomavirus is the most common sexually transmitted disease in the United States and is the leading cause of cervical cancer. Though most HPV infections are self limiting, 11,000 women will get cervical cancer this year. In an effort to reduce the burden of HPV due to its sequelae of genital warts, cervical lesions, and cervical cancer, a vaccine has been developed. Gardasil is a quadrivalent vaccine to prevent infection of 4 types of HPV. This 3 series vaccine schedule is recommended by the ACIP to be given to girls, in addition to their routine vaccinations, between the ages of 11 and 12 years. For females between 13 and 26 years of age who have not yet been vaccinated, are sexually active, or have been infected with HPV, vaccination is still recommended. Gardasil alone will not prevent all HPV infections; therefore, routine cancer screenings and pap smears are the best ways to reduce the incidence of cervical cancer.

Treatment Recommendations for Lyme Neuroborreliosis

Introduction
Lyme disease, caused by the tick borne spirochete Borrelia burgdorferi, is the most common vector borne disease in the United States with about 20,000 cases yearly. In the northeastern and north central United States, the blacklegged tick (deer tick, Ixodes scapularis) is responsible for the transmission of B. burgdorferi from infected mice, squirrels, and other small animals to humans. An increase in disease transmission correlates with the feeding habits of the blacklegged tick and usually peaks from May through September.

Erythema Migrans
After transmission of B. burgdorferi to the human host, an incubation phase occurs where the spirochete multiplies in the skin immediately surrounding the tick bite. Initially, pro-inflammatory cytokines are activated which produce the erythema migrans skin lesion that is characteristic of early stage Lyme disease. Erythema migrans lesions present in 70 to 80% of infected persons as a circular, flat, red rash that is painless and warm to the touch. As the rash expands over a period of days, the center may clear producing a bulls eye appearance. After a few days to weeks, B. burgdorferi spreads to multiple sites where additional erythema migrans skin lesions can be seen. Patients may also present with fatigue, headache, fever, chills, muscle and joint aches, and swollen lymph nodes. Diagnosis of Lyme disease is based on these characteristic findings and risk factors for being exposed to ticks, including exposure to heavily wooded areas in the northern and mid-Atlantic states, or exposure to animals that may have been in these areas.

Symptoms
Borrelia burgdorferi infection, if left untreated, could ultimately spread into other parts of the body within a few weeks causing sporadic bouts of arthritis in major joints, loss of muscle tone on both sides of the face (facial palsy), and generalized achiness. Months to years after the initial infection, 5% of patients will experience neuroborreliosis, a neurologic manifestation of the disease. Patients may present with sensory peripheral neuropathy and/or altered cognitive function. Upon examination, meningitis, cranial neuritis, radiculoneuritis (inflammation of spinal nerves), and inflammation of the brain or spinal cord may be seen.

Neuroborreliosis Treatment
Early stage Lyme disease can be successfully treated with oral doxycycline or amoxicillin. However, there is less definitive evidence on the best approach to treat nervous system Lyme disease. The results of a small Swedish study published in 1983 showed that intravenous (IV) penicillin was an effective treatment for Lyme disease. Since that time, various studies have been performed comparing the efficacy of multiple regimens with the goal of finding the best treatment for neuroborreliosis.
Intravenous Therapy
Currently, the majority of treatment regimens consist of parenteral administration of beta-lactam antibiotics. One recent study compared the use of ceftriaxone (2 g daily IV x 14 days) vs. penicillin (4 million units IV every 4 hours x 10 days) in the treatment of neuroborreliosis. Patients with active late stage Lyme disease were randomly assigned to 1 of the 2 treatments to assess any differences in the rate of response. Of the 23 patients with confirmed neuroborreliosis who entered the study, 10 were randomly assigned to the penicillin group and 13 were randomized to receive ceftriaxone. Treatment failure was defined as arthritis, peripheral neuropathy, or encephalopathy after 3 months of therapy. The results showed a slightly longer mean duration of disease in the penicillin treated group, but this difference was not statistically significant. However, differences were seen during post treatment follow-up exams. Fifty percent of patients in the penicillin treated group had symptoms of persistent disease including arthritis, fatigue, and, memory difficulty, compared to 10% of patients in the ceftriaxone group. One patient in the penicillin group had continuous peripheral neuropathy. Patients whose symptoms were unresponsive to penicillin were switched to ceftriaxone, and symptoms decreased. A follow-up study compared ceftriaxone doses of 2 g daily and 4 g daily for 14 days. This study showed no statistically significant difference between the groups as both doses were effective in treating the symptoms of neuroborreliosis. The results of these studies indicate that \textit{B. burgdorferi} shows better susceptibility to ceftriaxone than to penicillin.

Oral Therapy
Currently, there are no well designed published trials that demonstrate superiority of oral treatment for neuroborreliosis compared to IV. Doxycycline (200 mg daily orally for 14 days) is widely used in Europe. Pharmacologic studies in Europe have shown that oral doxycycline does exceed necessary minimum inhibitory concentrations in the cerebrospinal fluid to eradicate \textit{B. burgdorferi}. To date, it is unclear if this data can be extrapolated to the United States, due to different strains of the organism.

Corticosteroids have been used for treatment of neuroborreliosis especially in individuals that have facial palsy. Due to a lack of evidence for improving patient outcomes, treatment with corticosteroids in combination with antibiotics is not recommended.

Post-Lyme Disease Syndrome
Once treatment with antibiotics is complete, many patients experience post-Lyme disease syndrome which is associated with the prolonged occurrence of neuroborreliosis symptoms without active infection. A recent study was conducted to see if there was a reduction in post-Lyme disease symptoms with a second course of antibiotics compared to placebo. This study was stopped prematurely as the safety monitoring board stated that there was no likely difference between the groups. Furthermore, the group that was assigned antibiotics experienced an increase in adverse effects. Antibiotic treatment is not recommended for patients with post-Lyme disease syndrome. Current therapeutic recommendations include symptomatic treatment only.

Neuroborreliosis Treatment Guidelines from the American Academy of Neurology
Neuroborreliosis has been widely treated with beta-lactam antibiotics for some time. Recent studies have shown that 3\textsuperscript{rd} generation cephalosporins, in particular ceftriaxone, are the most effective treatment. The goal of therapy is eradication of \textit{B. burgdorferi} infection with any agent that will cause the lowest incidence of adverse effects and prevent the recurrence of symptoms long-term. After an extensive analysis of 37 articles relevant to the treatment of neuroborreliosis, the American Academy of Neurology developed treatment guidelines which are listed below.

The following dosage regimens are probably safe and effective treatments for neuroborreliosis:
- Ceftriaxone 2 g daily IV for 14 to 28 days
- Cefotaxime 2 g IV ever 8 hours for 14 to 28 days
- Penicillin G 18 to 24 M units daily divided every 4 hours for 14 to 28 days
- Doxycycline 100 mg orally twice daily

The following dosage regimens may be alternative treatments for neuroborreliosis but supporting data are lacking:
- Amoxicillin 500 mg three times daily
- Cefuroxime 500 mg twice daily

Summary
Although the incidence of neuroborreliosis secondary to Lyme disease is rare, it can be associated with significant morbidity due to complications such as sensory peripheral neuropathy and/or altered cognitive function. Treatment with beta-lactam antibiotics and 3\textsuperscript{rd} generation cephalosporins, in particular ceftriaxone, has been shown to be effective in preventing the reoccurrence of symptoms. The Academy of Neurology has published guidelines to aid healthcare professionals treating patients with neuroborreliosis.
P&T Committee Formulary Action

Additions
- Tobramycin injection – Restricted to presumed or documented *pseudomonas* infection

Line extensions
- Risperidone 0.25mg tablet
- Sevelamer 400mg tablet

Deletions
- Diazoxide injection

Authors:
Carissa E. Mancuso, PharmD
Cheryl L. Nunn-Thompson, Pharm.D., BCPS, M.B.A.
Amanda Ries, PharmD Candidate
Eric Haas, PharmD Candidate

Editor:
Carissa E. Mancuso, PharmD