## PRODUCT THEATER

### Examining Safety and Efficacy of Humira in Older Adults With Arthritis

Within the past 10 years, Humira (adalimumab) has been approved by the US Food and Drug Administration to treat rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. As adalimumab belongs to a relatively new class of drugs called biologics, its safety and efficacy have been of great interest in the research community, representing a new avenue of treatment for these and numerous other debilitating conditions. In a product theater at the ASCP meeting, Evan L. Siegel, MD, Arthritis and Rheumatism Associates, Rockville, MD, discussed Humira in the treatment of rheumatic diseases in the primary care setting. *Annals of Long-Term Care®* (*ALTC*) had the opportunity to interview Dr. Siegel about the indications of Humira and considerations before prescribing Humira to older adults.

***ALTC:* Briefly describe the mechanism of action of Humira.**
**Dr. Siegel:** Adalimumab is a fully human monoclonal antibody specific to tumor necrosis factor (TNF)-alpha. TNF-alpha is a cytokine, a molecule that allows cell-to-cell communication, which is essential during the initiation, maintenance, and amplification of an inflammatory response. Humira intercepts TNF-alpha both in serum and at the cell surface.

**Which patients are candidates for receiving Humira?**
Humira is indicated for the treatment of adult patients with psoriatic arthritis, ankylosing spondylitis, or moderate to severe rheumatoid arthritis. Of course, the first step is always to confirm the diagnosis. Joint and back pain can be related to many diagnoses other than those already mentioned, and each would be treated very differently. Patients with more than 6 weeks of chronic joint inflammation and swelling particularly in the hands and feet, or chronic inflammatory type back pain (worse with rest, better with activity) should be evaluated by a rheumatologist, if possible. Active disease may be manifest in many ways, depending on the disease: by ongoing peripheral joint inflammation with pain, tenderness and swelling; ongoing inflammatory back pain; erosive bone changes on radiography; or active psoriatic skin disease. Methotrexate is usually used as an initial disease-modifying antirheumatic drug in rheumatoid arthritis, but Humira may be appropriate as an initial agent in patients with ankylosing spondylitis or those with psoriatic arthritis.

**What are some of the screening and monitoring considerations for prescribing Humira to older adults?**
The list of potential side effects of adalimumab is long and beyond the scope of a short answer in this type of forum, but by far one of the most important adverse events to watch for is infection. TNF inhibition can allow for reactivation of latent tuberculosis, and all patients should be screened for tuberculosis before and intermittently during therapy with Humira, which is especially important in long-term care settings. Subclinical hepatitis must also be ruled out. Serious bacterial and fungal infections can occur at higher frequency and aggressive work-up of fever or other signs of infection is essential. In the elderly population, Humira should be used with caution due to a higher incidence of infections and malignancies. Additionally, congestive heart failure can be exacerbated by TNF inhibition, so these patients should be monitored carefully. There are many other potential side effects, so Humira should only be administered by a rheumatologist or other professional well-versed on the risk/benefit profile of Humira.

*This product theater was sponsored by Abbott Laboratories.*



### Dabigatran Etexilate Well Tolerated Following Knee or Hip Replacement Surgery

An open-label, prospective, observational study found that dabigatran etexilate was effective and well tolerated in patients undergoing total knee or hip replacement surgery.

The incidence of symptomatic venous thromboemolic events (VTEs) and all-cause mortality, the primary efficacy end point, was lower in patients who underwent total hip replacement surgery. The incidence of major bleeding events, the primary safety end point, was comparable in the two groups. Results were presented at the AHA meeting during a poster session.

In October 2010, the US Food and Drug Administration approved dabigatran etexilate to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The drug, a direct thrombin inhibitor, has also

been approved in more than 80 countries (not in the United States) for the primary prevention of VTEs after elective total knee or hip replacement surgery. The authors noted that phase 3 trials found 220 mg dabigatran etexilate taken daily was as effective as daily 40-mg doses of enoxaparin to prevent VTEs following total knee or hip replacement surgery.

> [Dabigatran] has been approved in more than 80 countries for the primary prevention of VTEs after elective total knee or hip replacement surgery.

In this study, 5292 patients between the ages of 18 and 75 years were treated with 220 mg dabigatran etexilate daily between March 2009 and July 2011. Exclusion criteria included concomitant amiodarone or quinidine treatment, an indication for quinidine or chronic anticoagulant therapy, renal or hepatic impairment, active clinically significant bleeding, or spontaneous or pharmacological impairment of haemostasis. All patients had three visits: at baseline (≤7 days before surgery); when discharged from the hospital or 24 to 48 hours after ending treatment (whichever came first); and at follow-up if they were discharged before finishing treatment.

Of the patients, 2734 underwent hip replacement surgery and 2558 underwent knee replacement surgery. The mean age was 62.6 years, 42.2% of patients were men, and 99.0% were white. The overall incidence of major bleeding events was 0.72% (95% confidence interval [CI], 0.51%-0.98%), and the incidence was similar in the hip replacement (0.69%; 95% CI, 0.42%-1.08%) and knee replacement (0.74%; 95% CI, 0.45%-1.16%) groups.

The authors defined *major bleeding events* as clinically overt bleeding; fatal, retroperitoneal, intracranial, intraocular, or intraspinal bleeding; or bleeding warranting treatment cessation or leading to reoperation.

In patients with at least one risk factor for bleeding, the incidence of major bleeding events was 0.76%, which was comparable to the 0.64% incidence among patients with no risk factors. The risk factors were active smoking, coronary artery disease, chronic heart failure, history of VTE, concomitant acetylsalicyclic acid use, and chronic use of nonsteroidal anti-inflammatory drugs.

An adverse event occurred in 18.7% of the population; 2.6% had a serious adverse event, and 4.9% had an adverse event that led to discontinuation of dabigatran etexilate. The incidence of symptomatic VTEs and all-cause mortality was 1.04% (95% CI, 0.78%-1.35%), including 0.55% (95% CI, 0.31%-0.90%) in patients undergoing hip replacement and 1.56% (95% CI, 1.12%-2.12%) in patients undergoing knee replacement.

Patients with a history of VTE had a higher incidence than those without a history of VTE (odds ratio, 5.59; 95% CI, 2.53-11.08). The authors noted none of the other risk factors had much of an impact on the incidence of symptomatic VTEs and all-cause mortality.—*Tim Casey*

*The study was sponsored by Boehringer Ingelheim.*

## Serelaxin Effective in Patients With Acute Heart Failure

Patients with acute heart failure who took serelaxin intravenously for 48 hours experienced an improvement in dyspnea, in-hospital signs and symptoms of acute heart failure, in-hospital worsening of heart failure, and 180-day cardiovascular and all-cause mortality compared with a placebo group, according to the results of RELAX-AHF (Relaxin in Acute Heart Failure), a phase 3, prospective, randomized, double-blind, placebo-controlled, parallel-group trial.

The serelaxin group had 45% fewer episodes of worsening heart failure symptoms during hospitalization and spent nearly a full day less in the hospital than those in the placebo group. The drug, a peptide hormone and a recombinant form of the human hormone relaxin-2, had no effect on rehospitalization rates, and it was deemed safe, demonstrating a similar profile to placebo.

John Teerlink, MD, the study's co-lead author and professor of medicine, University of California in San Francisco, presented the findings in a late-breaking abstract session at the AHA meeting. Results were also published in *The Lancet* (2013;381[9860]:29-39).

When introducing the trial, Teerlink explained that serelaxin is a derivative of relaxin, a pregnancy hormone. Pregnancy requires "tremendous" improvement in cardiac output and vascular and renal performance. In previous trials, relaxin mediated the adaptations associated with pregnancy and had anti-ischemic, anti-inflammatory, and antifibrotic effects. These principles were applied to RELAX-AHF.

The researchers began with a phase 2 pilot study of 234 patients that found the 30 µg/kg serelaxin daily led to improvement in dyspnea, provided other in-hospital benefits, and resulted in potential improvement in cardiovascular and all-cause survival. Teerlink added that the drug was safe and well tolerated with no significant adverse events.

Patients were included if they were 18 years of age or older (mean age, 72 years), hospitalized for acute heart failure, received at least 40 mg furosemide administered intravenously between the time of admission to emergency services and study screening, had systolic blood pressure above 125 mm Hg,

impaired renal function, and weighed less than 160 kg. The exclusion criteria included treatment with any intravenous therapies; stroke within 60 days; acute coronary syndrome within 45 days; major surgery within 30 days; and presence of acute myocarditis, significant valvular heart disease, or hypertrophic/restrictive/constrictive cardiomyopathy.

The authors randomized patients in a 1:1 ratio to receive 30 µg/kg serelaxin or placebo daily, administered intravenously for 48 hours. Patients were enrolled between October 2009 and February 2012 at 96 sites across 11 countries. They received the medication within 16 hours of hospitalization. Most patients had elevated systolic blood pressure (mean, 142 mm Hg).

Over an 180-day follow-up, there was a significant improvement favoring the serelaxin group in cardiovascular mortality (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.41-0.96; *P*=.028) as well as in all-cause death (HR, 0.63; 95% CI, 0.43-0.93; *P*=.02). There were also significant improvements in the signs and symptoms of congestion at day 2.

From baseline through day 5, there was a 19.4% increase in the area under the curve for dyspnea relief in patients who took serelaxin compared with placebo (*P*=.0075). Teerlink said that results showed serelaxin improved survival according to the authors' prespecified criteria. No significant difference in cardiovascular death or heart failure rehospitalization through day 60 was observed (HR, 1.02; 95% CI, 0.74-1.41; *P*=.89). There was a 30% reduction in cardiovascular deaths in the serelaxin group but a 20% increase in rehospitalizations in patients who took serelaxin, although the differences were not statistically significant.—*Tim Casey*

*The study was funded by Corthera, a Novartis affiliate company.*

## Use of Daily Multivitamin Does Not Reduce Risk of Cardiovascular Disease

Older male physicians who took a multivitamin every day for more than a decade had similar rates of major cardiovascular events, total myocardial infarction, and total stroke compared with a group that took a placebo, according to a randomized, double-blind, placebo-controlled, factorial design study.

Lead author Howard D. Sesso, MD, associate professor, Brigham and Women's Hospital, Boston, MA, presented the findings in a late-breaking abstract session at the AHA meeting. Results were simultaneously published online in the *Journal of the American Medical Association* (2012;308[17]:1751-1760). The trial was part of the Physicians' Health Study II that includes 14,641 male physicians in the United States who are 50 years of age or older. Of the participants, 7641 had enrolled in the Physicians' Health Study I from 1982 through 1996, during which they received aspirin and beta-carotene via mail to test if the products prevented cardiovascular disease and cancer. The remaining 7000 physicians were from part 2 of the study, which began in 1997 and is ongoing.

Sesso said more than half of adults in the United States take vitamin supplements, and more than one-third take multivitamins. He indicated that components of multivitamins might reduce the risk of cardiovascular disease, although observational studies have not demonstrated that association. This is the first large, long-term, randomized trial testing multivitamins in preventing cardiovascular disease and other chronic diseases, according to Sesso. He said the individual trials tested higher doses of vitamins and minerals, whereas multivitamins contain lower doses of the individual vitamins and minerals in combination.

Participants in the study took a multivitamin (n=7317) or placebo (n=7324) daily. Cardiovascular disease and cancer were the primary outcomes, while eye disease and cognitive function were secondary outcomes. The primary cardiovascular outcome was major cardiovascular events, defined as the composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death.

The researchers used a monthly calendar pack to help physicians adhere to their regimens. The mean follow-up was 11.2 years. At 4 years, 77% of participants adhered to the multivitamin regimen; at 8 years, the adherence rate was 72%; and at study end, the rate was 67%. The groups were well balanced. The mean age was 64 years, and mean body mass index was 26.0 kg/m$^2$. The participants were healthy: approximately 3.5% were smokers, 62% exercised at least once per week, 77% took aspirin, and daily intake of fruits and vegetables was higher compared with the general population, according to Sesso.

There were 876 major cardiovascular events in the multivitamin group and 856 in the placebo group (hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.91-1.10; *P*=.91). Total myocardial infarctions were 317 and 335, respectively (HR, 0.93; 95% CI, 0.80-1.91; *P*=.39), while instances of total stroke were 332 and 311, respectively (HR, 1.06; 95% CI, 0.91-1.23; *P*=.48).

There was also no effect for primary or secondary prevention of cardiovascular disease among participants with or without a history of cardiovascular disease. Sesso noted that there were 27 deaths due to myocardial infarction in the multivitamin group compared with 43 in the placebo group, which he deemed as a "borderline reduction" (HR, 0.61; 95% CI, 0.38-0.995; *P*=.048). "We had a very small number of events," Sesso said. "We consider that to be interesting but exploratory at this point."—*Tim Casey*

*The study was funded by the National Institutes of Health and the BASF Corporation. Study packaging was provided by DSM Nutritional Products Inc.*

## Pomalidomide and Low-Dose Dexamethasone Improves Outcomes in Elderly Patients With Multiple Myeloma

Patients with multiple myeloma who had primary refractory or relapsed and refractory disease had a significant improvement in progression-free and overall survival if they took pomalidomide plus low-dose dexamethasone compared with a group that received high-dose dexamethasone, according to a phase 3, prospective, randomized, open-label trial.

The combination group had a median progression-free survival of 3.6 months compared with 1.8 months for the high-dose dexamethasone group (hazard ratio [HR], 0.45; *P*<.001). Median overall survival was not reached in the combination group and was 7.8 months (HR, 0.53; *P*<.001) in the high-dose dexamethasone group.

The study's lead author, Meletios A. Dimopoulos, MD, chairman, Department of Clinical Therapeutics, University Athens School of Medicine, Athens, Greece, presented the results in a late-breaking abstract session at the ASH meeting.

Multiple myeloma, a cancer of the plasma cells, usually occurs in persons older than 50 years, and the incidence increases with age. There is no cure for the disease, thus treatment is targeted to improve pain, control complications, and slow disease progression. Dimopoulos said many patients with double refractory multiple myeloma are treated with high-dose dexamethasone, although there is no standard therapeutic option. Previous trials showed pomalidomide and low-dose dexamethasone were effective in relapsed or refractory multiple myeloma patients who received lenalidomide and/or bortezomib.

This is the first study to evaluate pomalidomide and low-dose dexamethasone versus high-dose dexamethasone in patients who are double refractory to lenalidomide and bortezomib, according to Dimopoulos. Pomalidomide is a novel oral immunomodulatory drug.

Patients were randomized in a 2:1 ratio to receive 4 mg daily pomalidomide for 3 weeks on followed by 1 week off plus weekly 40-mg doses of dexamethasone (n=302 patients) or high-dose mexathesone for 4 days on followed by 4 days off (n=153 patients). They received treatment until the researchers found disease progression or toxicity to the medications.

Inclusion criteria included patients who were refractory to their last therapy, had taken two or more prior therapies, had failed treatment with lenalidomide and bortezomib, and had primary refractory disease or relapsed and refractory disease.

The last of the 455 patients were enrolled on August 31, 2012, and the data cut-off was September 7, 2012, by which the occurrence of 242 events triggered the final progression-free survival analysis. There were also 106 events included for the interim overall survival analysis.

Median follow-up was 4 months, which Dimopoulos acknowledged was "very short." Of the patients, 34% were randomized from June 30, 2012, to August 31, 2012. During the final progression-free survival analysis, the data monitoring committee recommended that patients in the high-dose dexamethasone group who had not progressed be allowed to receive the combination treatment due to its superiority, according to Dimopoulos. He said 29% of patients chose to switch groups.

The baseline characteristics of the patients were similar: median age was approximately 65 years, median number of prior therapies was five, and median time from initial diagnosis to enrollment in the trial was 5.5 years. Of the patients in the high-dose dexamethasone group, 25% continued to receive treatment after the trial ended compared with 45% in the combination group.

> There is no cure for [multiple myeloma], thus treatment is targeted to improve pain, control complications, and slow disease progression.

The overall response rate was 21% in the combination group and 3% in the high-dose dexamethasone group (*P*<.001). Dimopoulos said the combination treatment led to a significant improvement in progression-free survival and overall survival regardless of the last prior treatment the patients received. It was also effective in patients with moderate renal impairment.

The most common grade 3 or 4 hematologic adverse event was neutropenia, found in 42% of patients in the combination group and 15% of patients who took high-dose dexamethasone. In addition, 7% of patients in the combination group and 6% of patients in the high-dose dexamethasone group discontinued the study due to an adverse event.—*Tim Casey*