

Acid Suppression Use Increases Hip Fracture Risk

BY ANN C. LOGUE
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CHICAGO — Long-term use of proton pump inhibitors, histamine₂-receptor antagonists, and other acid suppressors increases the risk of hip fracture, Yu-Xiao Yang, M.D., reported at the annual Digestive Disease Week.

Physicians turning to a combination of NSAIDs and protein pump inhibitors (PPIs) in place of cyclooxygenase-2 (COX-

2) inhibitors should be aware of this effect in patients who are at increased risk of osteoporosis, but they should not deny this therapy to patients with appropriate indications, said Dr. Yang of the division of gastroenterology at the University of Pennsylvania, Philadelphia.

PPIs interfere with calcium absorption, leading to an increased risk of hip fracture.

“Do patients with more than 1 year of PPI therapy have more hip fractures? Up until now, there has been no epidemiolog-

ical study to address this,” said Dr. Yang.

His conclusions came from a retrospective cohort study of 518,096 patients older than 40 years who were included in the U.K. General Practice Research Database between May 1987 and April 2002. Of these, 47,631 had more than 1 year of exposure to a PPI; the remaining 470,465 patients had no exposure to either a PPI or histamine₂-receptor antagonist (H2RA).

By looking at complete prescription information and validated hip fracture re-

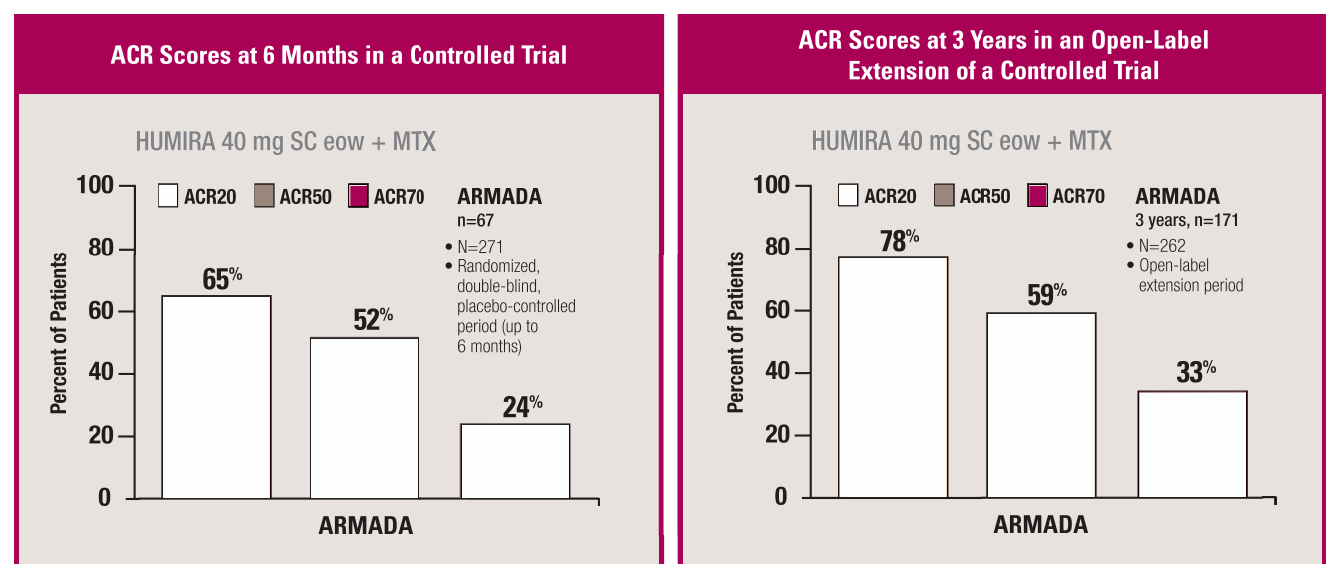
ports, the researchers discovered that taking a PPI long term was associated with an increased risk of hip fracture, with a relative risk of 1.9 associated with at least 1 year of PPI use.

The relationship had both a dose-response effect and a duration-response effect. H2RA use also increased the relative risk of hip fracture, but to a lesser extent, Dr. Yang noted.

In general, the PPI-exposed patients were sicker and took more medications, so

IT'S ABOUT RESPONSE

ACR SCORES MAINTAINED IN MODERATE-TO-SEVERE RA²⁻⁴



The above analysis is the intent-to-treat study population using nonresponder imputation methodology. Patients who withdrew or had missing values were considered nonresponders.

The above analysis is as-observed at the indicated time points. Patients with missing data were excluded.

TRIALS DESIGNED TO MATCH REAL-LIFE PATIENTS^{1,3-6}

BASELINE PATIENT DEMOGRAPHICS IN HUMIRA TRIALS ARMADA + DE019^{1,3-6}

- All trial patients had inadequate response to MTX
- Failed up to 3 DMARDs
- Disease duration (years): 10.0 to 12.5
- Mean HAQ DI: 1.4 to 1.6
- Mean CRP (mg/dL): 1.6 to 3.1

IMPORTANT SAFETY INFORMATION

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. **HUMIRA** can be used alone or in combination with MTX or other DMARDs.

TUBERCULOSIS (TB) AND INVASIVE OPPORTUNISTIC FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF-BLOCKING AGENTS, INCLUDING HUMIRA. PATIENTS SHOULD BE EVALUATED FOR LATENT (INACTIVE) TB WITH A SKIN TEST. TREATMENT OF TB SHOULD BE INITIATED PRIOR TO THERAPY WITH HUMIRA. THE BENEFITS AND RISKS OF HUMIRA SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF TREATMENT FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TB OR HISTOPLASMOSIS IS ENDEMIC.

SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF-BLOCKING AGENTS, INCLUDING HUMIRA. MANY OF THESE INFECTIONS OCCURRED IN PATIENTS PREDISPOSED TO INFECTIONS BECAUSE OF CONCOMITANT IMMUNOSUPPRESSIVE THERAPY IN ADDITION TO THEIR UNDERLYING DISEASE. PATIENTS WHO DEVELOP A NEW INFECTION WHILE USING HUMIRA SHOULD BE MONITORED CLOSELY. TREATMENT SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. DO NOT START HUMIRA IN PATIENTS WITH ACTIVE

INFECTION (INCLUDING CHRONIC OR LOCALIZED), OR ALLERGY TO HUMIRA OR ITS COMPONENTS. EXERCISE CAUTION IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR WITH UNDERLYING CONDITIONS, WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS.

The combination of HUMIRA and anakinra is not recommended. TNF-blocking agents, including HUMIRA, have been associated in rare cases with exacerbation of demyelinating disease. Exercise caution when considering HUMIRA for patients with these disorders. Lymphoma has been observed in patients treated with TNF-blocking agents. The role of TNF-blocking agents in the development of malignancy is not known.

Anaphylaxis has been reported rarely following HUMIRA administration. Rare reports of pancytopenia including aplastic anemia have been reported with TNF-blocking agents. Medically significant cytopenia (e.g. thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Worsening congestive heart failure (CHF) has been observed with TNF-blocking agents, including HUMIRA, and new onset CHF has been reported with TNF-blocking agents.

Most frequent adverse events vs placebo from placebo-controlled studies were injection site reactions (20% vs 14%), upper respiratory infection (17% vs 13%), injection site pain (12% vs 12%), headache (12% vs 8%), rash (12% vs 6%), and sinusitis (11% vs 9%). Discontinuations due to adverse events were 7% for HUMIRA vs 4% for placebo.

potential confounders were considered and adjusted for if they represented markers of comorbidity status or if they had an effect on the central nervous system that would increase the risk of falling, Dr. Yang noted in his presentation.

After adjustment for potential confounders, there was still a significantly increased risk of hip fracture among long-term PPI users. Significant confounders included antidepressant use and an increased number of office visits.

The study was limited by the assumption of 100% compliance with therapy and the lack of information on use of over-the-counter drugs, Dr. Yang said. ■

Weekly Bisphosphonate Compliance Suboptimal

WASHINGTON — Osteoporosis patients demonstrate greater compliance with weekly bisphosphonate therapy than with daily medication, but the numbers are still suboptimal, Deborah T. Gold, Ph.D., reported in a poster she presented at an international symposium sponsored by the National Osteoporosis Foundation.

Patients often resist taking bisphosphonates because of their inconvenient and complex dosing procedures, explained Dr. Gold of Duke University Medical Center, Durham, N.C.

Dr. Gold and her associates analyzed data on 214,060 women aged 50 years and older who received bisphosphonate therapy; the information had been collected for two health claims and retail pharmacy databases. Overall, weekly doses led to improved compliance after 1 year, compared with daily doses (44%-55% vs. 32%-40%), but 42%-67% of the patients on the weekly regimen had discontinued the medication within a year.

In addition, the level of compliance with either a weekly or daily dose was of-

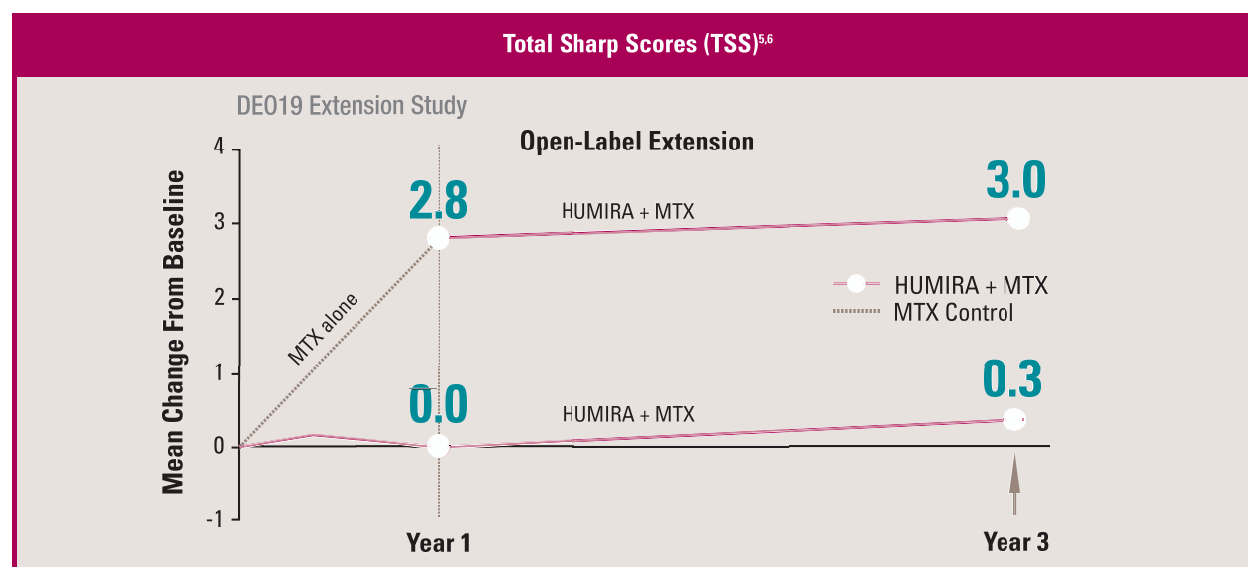
ten too low to benefit many patients. Sufficient compliance was defined as a "medication possession ratio" of at least 80%. At most, only 53% of patients who received weekly medication were deemed compliant enough to derive antifracture benefits from it, which was still significantly better than the up to 40% rate of sufficient compliance among patients who received daily medication. Dr. Gold serves as a consultant for multiple pharmaceutical companies.

—Heidi Splete

IT'S ABOUT

RADIOGRAPHIC EVIDENCE

INHIBITION OF DISEASE PROGRESSION IN MODERATE-TO-SEVERE RA^{5,6}



Year 1 and year 3 x-rays were assessed for changes from baseline in TSS.

Study DE019-619 patients entered a randomized, double-blind, placebo-controlled period up to 1 year. 457 patients entered the open-label extension period.

- In the DE019 extension study, a majority of patients continued to show *no radiographic progression* (≤ 0.5 -unit increase from baseline) at 3 years ($n=129$)⁶
 - 61% based on Total Sharp score (mean change=0.3)
 - 71% based on Joint Erosion score (mean change=0.1)
 - 73% based on Joint Space Narrowing score (mean change=0.2)

HUMIRA[®]
(adalimumab)

References: 1. Data on File. Abbott Laboratories. 2. HUMIRA full prescribing information. 3. Weinblatt ME, Keystone EC, Furst DE, et al. The ARMADA trial: sustained efficacy and long-term safety of adalimumab (HUMIRA[®]) plus methotrexate over 3 years in patients with long-standing rheumatoid arthritis. Presented at: European League Against Rheumatism Annual Scientific Meeting; June 2004; Berlin, Germany. 4. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate. *Arthritis Rheum.* 2003;48:35-45. 5. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes

of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. *Arthritis Rheum.* 2004;50:1400-1411. 6. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic inhibition of structural damage sustained in patients with long-standing rheumatoid arthritis following 3 years of treatment with adalimumab (HUMIRA[®]) plus methotrexate. Presented at: American College of Rheumatology Annual Scientific Meeting; October 2004; San Antonio, Tex.

Please see brief summary of prescribing information on adjacent page.