

Albumin, T3 Deficiencies Tied to Fracture Risk

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HARROGATE, ENGLAND — Low serum albumin and T3 levels are independently predictive of vertebral fractures in women older than 50 years, a 10-year prospective study has shown.

Because albumin and T3 deficiencies are considered markers of frailty and sickness, the findings suggest that chronic poor health may itself be a risk factor for

vertebral fracture, said Judith Finigan, principal investigator and research nurse in the bone metabolism group at the University of Sheffield (England).

To identify predictors of fracture in women between ages 50 and 85, the Sheffield investigators acquired baseline bone mineral density (BMD) measures and medical and lifestyle information from a population-based group of 375 women. They also collected fasting blood samples for measuring serum calcium, alkaline

phosphatase, parathyroid hormone, creatinine, phosphate, albumin, and thyroid hormones.

All participants had spinal radiographs taken at baseline and at years 2, 5, 7, and 10, which were reviewed for incident vertebral fractures by a single radiologist. Nonvertebral fractures were confirmed by radiologist reports.

Cox regression analysis showed that numerous risk factors—including age; BMD at the lumbar spine, hip, or total body;

years of estrogen exposure; and prevalent vertebral fracture—predicted fractures overall.

Low serum T3, low serum albumin, and low body fat were specifically predictive of vertebral fractures but not nonvertebral fractures. These measures remained significantly predictive, even after adjusting for age. Ms. Finigan reported at the annual conference of the National Osteoporosis Society. Neither TSH nor T4 predicted fracture, she noted.

The age-adjusted relative risks per standard deviation decrease for T3, albumin, and body fat were 1.71, 1.74, and 1.55, respectively. "T3 and albumin also predicted vertebral fracture independently of spine or hip BMD," said Ms. Finigan.

In a separate analysis of a larger cohort, the investigators examined the relationship between serum albumin and vertebral fractures in postmenopausal women from the placebo arms of the Hip Intervention Program (HIP) trial and the Vertebral Efficacy with Risedronate Therapy (VERT) trial.

At 3 years, 381 of 2,720 subjects had experienced one or more incident vertebral fractures. A multiple stepwise logistic regression analysis showed a 1.23 relative risk of vertebral fracture for each standard deviation decrease in serum albumin, after adjusting for femoral neck BMD, weight, and age.

As in the smaller study, low serum albumin was not associated with an increased risk of incident nonvertebral fractures in the larger population.

"The findings of the second analysis confirm the association between low baseline albumin levels and incident vertebral fractures," Ms. Finigan said.

Serum albumin and thyroid hormone measurements are recommended as part of a routine evaluation for osteoporosis in postmenopausal women. Patients with deficiencies in these may be candidates for antiresorptive treatment to reduce their risk of vertebral fractures, Ms. Finigan concluded.

VERBATIM

This 'is clearly the most definitive study to date looking at acupuncture for arthritis.'

Dr. Sharon Kolanski, on the findings of an NIH-sponsored trial, page 3

BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

HUMIRA™ (adalimumab)

WARNING

RISK OF INFECTIONS

Cases of tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) have been observed in patients receiving HUMIRA.

Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA.

CONTRAINDICATIONS

HUMIRA should not be administered to patients with known hypersensitivity to HUMIRA or any of its components.

WARNINGS

SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF T3 BLOCKING AGENTS INCLUDING HUMIRA. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS. TUBERCULOSIS AND INVASIVE OPPORTUNISTIC FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH T3 BLOCKING AGENTS INCLUDING HUMIRA.

TREATMENT WITH HUMIRA SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH HUMIRA SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF HUMIRA SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF HUMIRA IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR UNDERLYING CONDITIONS WHICH MAY PREDISPOSE THEM TO INFECTIONS. DRUG PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TUBERCULOSIS AND HISTOPLASMA ARE ENDEMIC (see PRECAUTIONS - Tuberculosis and Adverse Reactions - Infections). THE BENEFITS AND RISKS OF HUMIRA TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF HUMIRA THERAPY.

Neurologic Events: Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of HUMIRA in patients with pre-existing or recent central nervous system demyelinating disorders.

Malignancies: Lymphomas have been observed in patients treated with TNF blocking agents including HUMIRA. In clinical trials, patients treated with HUMIRA had a higher incidence of lymphoma than the expected rate in the general population (see ADVERSE REACTIONS-Malignancies). While patients with rheumatoid arthritis and other chronic active diseases, may be at a higher risk (up to several fold) for the development of lymphoma, the role of TNF blockers in the development of malignancy is not known.

PRECAUTIONS

General: Allergic reactions have been observed in approximately 1% of patients receiving HUMIRA. If an anaphylactic reaction or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy initiated.

Information to Patients: The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of HUMIRA. A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

Tuberculosis: As observed with other TNF blocking agents, tuberculosis associated with the administration of HUMIRA in clinical trials has been reported (see WARNINGS). While cases were observed at all doses, the incidence of tuberculosis reactions was particularly increased at doses of HUMIRA that were higher than the recommended dose. All patients recovered after standard antimicrobial therapy. No deaths due to tuberculosis occurred during the clinical trials.

Before initiation of therapy with HUMIRA, patients should be evaluated for active or latent tuberculosis infection with a tuberculin skin test. If latent infection is diagnosed, appropriate prophylaxis in accordance with the Centers for Disease Control and Prevention guidelines should be instituted. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of tuberculosis occur.

Immunosuppression: The possibility exists for T3 blocking agents, including HUMIRA, to affect host defense against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with HUMIRA, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocytes/macrophages, and neutrophils. The impact of treatment with HUMIRA on the development and course of malignancies, as well as active and/or chronic infections is not fully understood (see WARNINGS, ADVERSE REACTIONS, Infections and Malignancies). The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

Immunizations: No data are available on the effects of vaccination in patients receiving HUMIRA. Live vaccines should not be given concurrently with HUMIRA. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

Autolymism: Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome.

If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, treatment should be discontinued (see ADVERSE REACTIONS, Autoantibodies).

Drug Interactions: HUMIRA has been studied in rheumatoid arthritis patients taking concomitant MTX. The data do not suggest the need for dose adjustment of either HUMIRA or MTX. Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

Pregnancy: Pregnancy Category B - An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (265 times human AUC when given 40 mg subcutaneous with MTX every week or 373 times human AUC when given 40 mg subcutaneous without MTX) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of HUMIRA in pediatric patients have not been established.

Geriatric Use: A total of 519 patients 65 years of age and older, including 107 patients 75 years and older, received HUMIRA in clinical studies. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

ADVERSE REACTIONS

General: The most serious adverse reactions were (see WARNINGS):

- Serious Infections
- Neurologic Events
- Malignancies

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain) compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of Studies I, II, III, and IV was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse events leading to discontinuation of HUMIRA were clinical fever (0.7%), rash (0.3%) and pneumonia (0.3%).

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Infections: In placebo-controlled trials, the rate of infection was 1 per patient year in the HUMIRA treated patients and 0.9 per patient year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract and urinary tract infections. Most patients continued on HUMIRA after the infection resolved. The incidence of serious infections was 0.04 per patient year in HUMIRA treated patients and 0.02 per patient year in placebo-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis (see WARNINGS).

Thirteen cases of tuberculosis, including miliary lymphatic, peritoneal, and pulmonary were reported in clinical trials. Most of the tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Six cases of invasive opportunistic infections caused by histoplasma, aspergillus, and nocardia were also reported in clinical trials (see WARNINGS).

Malignancies: Among 2468 rheumatoid arthritis patients treated in clinical trials with HUMIRA for a median of 24 months, 48 malignancies of various types were observed, including 10 patients with lymphoma. The Standardized Incidence Ratio (SIR) (ratio of observed rate to age-adjusted expected frequency rate in the general population) for malignancies was 1.0 (95% CI, 0.7, 1.3) and for lymphomas was 5.4 (95% CI, 2.6, 10.0). An increase of up to several fold in the rate of lymphomas has been reported in the rheumatoid arthritis patient population, and may be further increased in patients with more severe disease activity (see WARNINGS-Malignancies). The other malignancies observed during use of HUMIRA were breast, colon-rectum, uterine-cervical, prostate, melanoma, gallbladder-bile ducts, and other carcinomas.

Autoantibodies: In the controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients had had positive baseline ANA titers developed positive titers at week 24. One patient out of 2334 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Immunogenicity: Patients in Studies I, II, and III were tested at multiple time points for antibodies to adalimumab during the 6 to 12 month period. Approximately 5% (58 of 1,062) of adult rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant MTX had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse events was observed. With monotherapy, patients develop-

ing every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions: The data described below reflect exposure to HUMIRA in 2334 patients, including 2073 exposed for 6 months, 147 exposed for greater than one year and 1300 in adequate and well-controlled studies (Studies I, II, III, and IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week. Table 1 summarizes events reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. Adverse event rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week.

Table 1: Adverse Events Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Periods of Rheumatoid Arthritis Studies

Adverse Event (Preferred Term)	HUMIRA 40 mg subcutaneous Every Other Week (N=2073)		Placebo (N=600)	
	Percentage	Percentage	Percentage	Percentage
Respiratory				
Upper respiratory infection	17	13	8	11
Sinusitis	11	6	6	6
Flu syndrome	7	7	6	6
Gastrointestinal				
Abdominal pain	9	8	4	4
Laboratory Tests*				
Laboratory test abnormal	8	7	4	4
Hypercholesterolemia	6	4	4	4
Hyperlipidemia	7	5	4	4
Hematology	4	4	4	4
Alkaline phosphatase increased	5	3	3	3
Other				
Injection site pain	12	12	12	12
Headache	12	8	8	8
Rash	12	6	6	6
Accidental injury	8	4	4	4
Injection site reaction**	8	1	1	1
Back pain	6	4	4	4
Urinary tract infection	6	4	4	4
Hypertension	5	3	3	3

* Laboratory test abnormalities were reported as adverse events in European trials.

** Does not include erythema and/or itching, hemorrhage, pain or swelling.

Other Adverse Events: Other infrequent serious adverse events occurring at an incidence of less than 5% in patients treated with HUMIRA were:

Body As A Whole: Fever, infection, pain in extremity, pelvic pain, sepsis, surgery, thorax pain, tuberculosis, reactivated

Cardiovascular System: Arrhythmia, atrial fibrillation, cardiovascular disorder, chest pain, congestive heart failure, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarction, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, vascular disorder

Collagen Disorder: Lupus erythematosus syndrome

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, granulocytopenia, leukopenia, lymphoma like reaction, pancytopenia, polythemia

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myositis, myogenic arthritis, myositis, tendon disorder

Neoplasms: Adenoma, carcinoma such as breast, gastrointestinal, skin, uterine, and/or other; lymphoma and melanoma

Nervous System: Confusion, multiple sclerosis, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung disorder, upper respiratory tract infection, pneumonia

Skin And Appendages: Cellulitis, kidney cysts, herpes zoster

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder, pyelonephritis

OVERDOSAGE: The maximum tolerated dose of HUMIRA has not been established in humans. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

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