

Better Bone Biomarkers on the Distant Horizon

BY JEFF EVANS
Senior Writer

BETHESDA, MD. — Fracture will continue to be the primary end point in clinical trials of treatments for osteoporosis until new biomarkers can stand in as surrogates for fracture, according to speakers at a meeting on bone quality.

The large number of factors that need to be tested to validate a single biomarker as a surrogate end point make it unlikely

that any single biomarker will adequately predict the risk of fracture, said Henry Bone, M.D., of the Michigan Bone and Mineral Clinic, Detroit. Researchers may need to combine a set of biomarkers into a model to produce the best surrogate.

Many new potential biomarkers of bone quality are being evaluated in small subgroups in clinical trials, but no single study has compared a set of bone quality measurements with bone mineral density (BMD) and radiographs for prediction of

fractures and the effect of treatment, Dr. Bone said. “We really haven’t considered using combined models integrating a number of different kinds of these intermediate end points or biomarkers.”

“For something as complicated as fracture risk, I think this is where we’re going to end up—that we use combinations of anatomical and more dynamic measurements in order to explain the effects of treatment,” added Steven R. Cummings, M.D., of the California Pacific Medical

Center Research Institute in San Francisco.

Surrogate end points, which may be faster and easier to measure than clinical outcomes such as fracture, could allow researchers to speed up clinical trials, enroll fewer patients into studies, and lower the cost of drug development, said Theresa Kehoe, M.D., of the division of metabolic and endocrine drug products at the Food and Drug Administration’s Center for Drug Evaluation and Research.

A surrogate end point in a clinical trial is a laboratory or radiologic measurement or physical sign—a biomarker—used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions, or survives. The changes induced by a therapy on this surrogate end point are expected to reflect changes in a clinically meaningful end point, such as fracture, Dr. Kehoe said.

In osteoporosis clinical trials involving the prevention of postmenopausal osteo-



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DR. BONE

porosis with estrogens, current regulatory practice permits the use of BMD data alone to act as a surrogate end point, Dr. Kehoe said at the meeting, which was sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the American Society for Bone and Mineral Research.

But data on the rate of fracture are necessary for clinical trials of the prevention or treatment of postmenopausal osteoporosis with selective estrogen receptor modulators or nonestrogen products. In those trials, Dr. Kehoe said the FDA “tends not to accept” BMD data as a surrogate for prevention of postmenopausal osteoporosis before it has data on the rate of fracture.

BMD is still the primary end point for efficacy in noninferiority trials that compare a once-daily formulation of a drug that has already been approved based on its ability to reduce the rate of fracture with a new formulation of the same drug, she said.

Dr. Kehoe raised additional questions to consider about surrogate end points:

► Should the surrogate show consistent sensitivity and specificity in more than one therapeutic class of drugs? A single negative therapeutic example has the potential to undermine the biological plausibility of the proposed surrogate, she noted.

► What type of fracture should the surrogate be tested against? This could be an asymptomatic morphometric vertebral fracture, which some already consider to be a surrogate for a symptomatic fracture.

► Should the surrogate have equal sensitivity and specificity for mild, moderate, and severe vertebral fractures?

► What sensitivity, specificity, positive and negative predictive values, or other relevant statistics should be required to prove that a surrogate is valid?

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HUMIRA® (adalimumab)

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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

SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF 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 TNF 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, OR 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.

Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blocking agents. Therefore, the combination of HUMIRA and anakinra is not recommended (see PRECAUTIONS, Drug Interactions).

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 preexisting or recent-onset central nervous system demyelinating disorders.

Malignancies: In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with moderately to severely active rheumatoid arthritis, 2 lymphomas were observed among 1380 HUMIRA-treated patients versus 0 among 690 control patients (mean duration of controlled treatment approximately 7 months). In the controlled and open-label portions of these clinical trials of HUMIRA in rheumatoid arthritis patients, 10 lymphomas were observed in 2468 patients over 4870 patient-years of therapy. This is approximately 5-fold higher than expected in the general population. Rates in clinical trials for HUMIRA cannot be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma. The potential role of TNF blocking therapy in the development of malignancies is not known. (see ADVERSE REACTIONS: Malignancies).

Hypersensitivity Reactions: In postmarketing experience, anaphylaxis has been reported rarely following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy instituted. In clinical trials of HUMIRA, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

Hematologic Events: Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA (see ADVERSE REACTIONS, Other Adverse Reactions). The causal relationship of these reports to HUMIRA remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

PRECAUTIONS

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 (see HUMIRA, PATIENT INFORMATION LEAFLET). 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 reactivations 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 a tuberculosis infection occur. Patients with Heart Failure: Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse events was observed. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Immunosuppression: The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses 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, monocyte/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.

Autoimmunity: 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

Methotrexate

HUMIRA has been studied in rheumatoid arthritis patients taking concomitant MTX (see CLINICAL PHARMACOLOGY: Drug Interactions). The data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF-blocking agents, including HUMIRA, may also result in similar toxicities (see WARNINGS, SERIOUS INFECTIONS).

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 (266 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 (adalimumab) should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

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 or swelling), 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 flare reaction (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 infections, bronchitis 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 military, lymphatic, peritoneal, and pulmonary, were reported in clinical trials. Most of the cases of 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 with moderately to severely active disease treated with HUMIRA in clinical trials for a mean of 24 months (4870 patient-years of therapy), 10 lymphomas were observed for a rate of 0.21 cases per 100 patient-years. This is approximately 5-fold higher than expected in an age- and sex-matched general population based on the Surveillance, Epidemiology, and End Results Database. Rates in clinical trials for HUMIRA cannot be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. (see WARNINGS: Malignancies). An increased rate of lymphoma has been reported in the rheumatoid arthritis patient population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma. The potential role of TNF-blocking therapy in the development of malignancies is not known. Thirty-eight malignancies, other than lymphoma, were observed. Of these, the most common malignancies were breast, colon, prostate, and uterine, which were similar in type and number to what would be expected in the general population.

Autoantibodies: In the controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative 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 1062) 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 receiving 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 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 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 4 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. In Study III, the types and frequencies of adverse events in the second year open-label extension were similar to those observed in the one-year double-blind period.

Table 4: Adverse Events Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

Adverse Event (Preferred Term)	HUMIRA	Placebo
	40 mg subcutaneous Every Other Week (N=705)	(N=690)
	Percentage	Percentage
Respiratory		
Upper respiratory infection	17	13
Sinusitis	11	9
Flu syndrome	7	6
Gastrointestinal		
Nausea	9	8
Abdominal pain	7	4
Laboratory Tests*		
Laboratory test abnormal	8	7
Hypercholesterolemia	6	4
Hyperlipidemia	5	4
Hematuria	7	5
Alkaline phosphatase increased	5	3
Other		
Injection site pain	12	12
Headache	12	8
Rash	12	6
Accidental injury	10	8
Injection site reaction**	8	1
Back pain	8	4
Urinary tract infection	6	5
Hypertension	5	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 infarct, 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, polycythemia (see WARNINGS, Hematologic Events)

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, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma, carcinomas such as breast, gastrointestinal, skin, urogenital, and others; lymphoma and melanoma.

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

Respiratory System: Asthma, bronchospasm, dyspnea, lung disorder, lung function decreased, pleural effusion, pneumonia

Skin And Appendages: Cellulitis, erysipelas, herpes zoster

Special Senses: Cataract

Thrombosis: Thrombosis leg

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

Adverse Reaction Information from Spontaneous Reports:

Adverse events have been reported during post-approval use of HUMIRA. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Hematologic Events: Thrombocytopenia (see WARNINGS, Hematologic Events).

Hypersensitivity reactions: Anaphylaxis (see WARNINGS, Hypersensitivity Reactions).

Skin reactions: cutaneous vasculitis.

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.

Revised: July 2004

Ref. 03-5364-R6

U.S. Govt. Lic. No. 0043

058-640-H547-1 MASTER

ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.

058-640-H571-1
PRINTED IN U.S.A.