

Hip Fractures Constant Despite Tranquilizer Cuts

BY BARBARA RUTLEDGE

Contributing Writer

Reduced use of benzodiazepines in elderly patients does not necessarily result in a lower incidence of hip fracture, according to a study by Anita Wagner, Pharm.D., of the department of ambulatory care and prevention at Harvard Medical School, Boston, and her colleagues.

The researchers found no significant difference in the incidence of hip fracture

over a 3-year period between elderly Medicaid recipients in New York, where benzodiazepine use decreased sharply during the study period, and in New Jersey, where benzodiazepine use remained constant.

"Benzodiazepines may not actually be associated with hip fractures, or at least not to the extent reported in some studies," Dr. Wagner and her colleagues wrote (Ann. Intern. Med. 2007;146:96-103).

The Prescription Drug Improvement and Modernization Act that went into effect in

January 2006 further restricted benzodiazepine prescription coverage for Medicare recipients. Federal policy makers may have expected that reduced benzodiazepine access would decrease hip fracture risk and thereby improve quality of life in the elderly.

"According to our analyses, this expectation may not be justified," Dr. Wagner and her associates concluded.

Earlier studies had suggested that benzodiazepine use might increase the risk of hip fracture in elderly patients, with pos-

tural imbalance associated with benzodiazepine use possibly leading to more falls and hip fractures in a population already at risk for hip fracture. But studies seeking to document a direct link have yielded conflicting results.

Since 1989, physicians in New York have been required to use serially numbered, triplicate forms for benzodiazepine prescriptions, with the third copy to be forwarded by the pharmacy to the state health authorities.

The study compared the risk of hip fractures in 1988 cohorts of 51,529 elderly Medicaid recipients in New York and 42,029 in New Jersey, where the prescription policy was unchanged.

In New York, the change in prescription policy led to an abrupt decline in benzodiazepine use, decreasing from

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about 40% of Medicaid enrollees each month in the 12-month period before the policy change to about 15% during the 21 months after the policy change. Benzodiazepine use among New Jersey Medicaid enrollees did not change significantly.

In New York, a total of 199 hip fractures occurred in female benzodiazepine recipients over the 33-month study period, with an increase in hazard rate from 53 per 100,000 enrollees before the policy change to 72 per 100,000 enrollees after the policy change.

In New Jersey, 135 hip fractures occurred in female benzodiazepine recipients in the study period, with a similar increase in hazard rate from 42 per 100,000 enrollees to 58 per 100,000 enrollees. A total of 30 hip fractures in male benzodiazepine recipients in New York occurred over the study period, with the hazard rate increasing from 38 per 100,000 enrollees before the policy change to 54 per 100,000 enrollees after the policy change. New Jersey results were similar, with a total of 27 hip fractures among male benzodiazepine recipients and an increase in hazard rate from 48 per 100,000 enrollees before the policy change in New York to 52 per 100,000 enrollees. In each case, hazard rates among benzodiazepine nonrecipients were similar.

No evidence suggests that the study results were skewed by disproportionate reductions in benzodiazepine use among different patient subgroups. After the policy change, there was no significant increase in the prevalence of higher-dose benzodiazepine prescriptions, and the increase in nonbenzodiazepine sedatives was modest.

The most likely explanation for the lack of decrease in hip fractures following decreased benzodiazepine use is simply that benzodiazepine use does not increase the risk of hip fracture in the elderly, Dr. Wagner and her colleagues wrote. ■

ORENCIA® (abatacept) Rx only

Brief Summary of Prescribing Information. For complete prescribing information please consult official package circular.

INDICATIONS AND USAGE: ORENCIA (abatacept) is indicated for reducing signs and symptoms, inducing major clinical response, slowing 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, such as methotrexate or TNF antagonists. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

ORENCIA should not be administered concomitantly with TNF antagonists. ORENCIA is not recommended for use concomitantly with anakinra.

CONTRAINDICATIONS: ORENCIA should not be administered to patients with known hypersensitivity to ORENCIA or any of its components.

WARNINGS: Concomitant Use with TNF Antagonists: In controlled clinical trials, patients receiving concomitant ORENCIA and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively) (see **ADVERSE REACTIONS: Infections**). These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonist; therefore, concurrent therapy with ORENCIA and a TNF antagonist is not recommended. While transitioning from TNF antagonist therapy to ORENCIA therapy, patients should be monitored for signs of infection.

PRECAUTIONS: Hypersensitivity: Of 2688 patients treated with ORENCIA in clinical trials, there were two cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction (see **ADVERSE REACTIONS: Infusion-Related Reactions and Hypersensitivity Reactions**).

Infections: Physicians should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infections, underlying conditions which may predispose them to infections, or chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment with ORENCIA should be monitored closely. Administration of ORENCIA should be discontinued if a patient develops a serious infection (see **ADVERSE REACTIONS: Infections**). A higher rate of serious infections has been observed in patients treated with concurrent TNF antagonists and ORENCIA (see **WARNINGS: Concomitant Use with TNF Antagonists**). Prior to initiating immunomodulatory therapies, including ORENCIA, patients should be screened for latent tuberculosis infection with a tuberculin skin test. ORENCIA has not been studied in patients with a positive tuberculin skin test, and the safety of ORENCIA in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with ORENCIA.

Immunizations: Live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ORENCIA. The efficacy of vaccination in patients receiving ORENCIA is not known. Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations.

Use in Patients with Chronic Obstructive Pulmonary Disease (COPD): COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. Use of ORENCIA in patients with rheumatoid arthritis and COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status (see **ADVERSE REACTIONS: Adverse Reactions in Patients with COPD**).

Information for Patients: Patients should be provided the ORENCIA Patient Information leaflet and provided an opportunity to read it prior to each treatment session. Because caution should be exercised in administering ORENCIA to patients with active infections, it is important that the patient's overall health be assessed at each visit and any questions resulting from the patient's reading of the Patient Information be discussed.

Drug Interactions: Formal drug interaction studies have not been conducted with ORENCIA. Population pharmacokinetic analyses revealed that MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance (see **CLINICAL PHARMACOLOGY: Pharmacokinetics** in Full Prescribing Information). The majority of patients in RA clinical studies received one or more of the following concomitant medications with ORENCIA: MTX, NSAIDs, corticosteroids, TNF blocking agents, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sulfasalazine, and anakinra.

Concurrent administration of a TNF antagonist with ORENCIA has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone. Concurrent therapy with ORENCIA and TNF antagonists is not recommended (see **WARNINGS: Concomitant Use with TNF Antagonists**).

There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with anakinra, and therefore such use is not recommended.

Immunosuppression: The possibility exists for drugs inhibiting T cell activation, including ORENCIA, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses. The impact of treatment with ORENCIA on the development and course of malignancies is not fully understood (see **ADVERSE REACTIONS: Malignancies**). In clinical trials, a higher rate of infections was seen in ORENCIA-treated patients compared to placebo (see **ADVERSE REACTIONS: Infections**).

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a mouse carcinogenicity study, weekly subcutaneous injections of 20, 65, or 200 mg/kg of abatacept administered each week for up to 84 weeks in males and 88 weeks in females were associated with increases in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females). The mice from this study were infected with murine leukemia virus and mouse mammary tumor virus. These viruses are associated with an increased incidence of lymphomas and mammary gland tumors, respectively, in immunosuppressed mice. The doses used in these studies were 0.8-, 2.0- and 3.0-fold, the human exposure at 10 mg/kg, respectively, based on AUC. The relevance of these findings to the clinical use of ORENCIA is unknown.

In a one-year toxicity study in cynomolgus monkeys, abatacept was administered intravenously once weekly at doses up to 50 mg/kg (9-fold the human exposure at 10 mg/kg dose based on AUC). Abatacept was not associated with any significant drug-related toxicity. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in immunosuppressed monkeys within the time frame of this study. The relevance of these findings to the clinical use of ORENCIA is unknown.

No mutagenic potential of abatacept was observed in the *in vitro* reverse Ames or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation (with or without metabolic activation) assays, and no chromosomal aberrations were observed in human lymphocytes (with or without metabolic activation) treated with abatacept. In rats, abatacept had no adverse effects on male or female fertility at doses up to 200 mg/kg every three days (11-fold a human dose based on AUC).

Pregnancy Category C: Abatacept was found not to be teratogenic in mice at doses up to 300 mg/kg and in rats and rabbits at doses up to 200 mg/kg daily (29-fold a human 10 mg/kg dose based on AUC in rats and rabbits). Rats treated with abatacept every three days during early gestation throughout the lactation period showed no adverse effects in the offspring at doses up to 45 mg/kg (3-fold a human 10 mg/kg dose based on AUC). At a dose of 200 mg/kg (11-fold a human 10 mg/kg dose based on AUC), alterations of immune function consisted of a 9-fold increase in the T-cell dependent antibody response in female pups and inflammation of the thyroid in one female pup out of 10 males and 10 females evaluated. Whether these findings indicate a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept has not been determined. Abatacept was shown to cross the placenta. Because animal reproduction studies are not always predictive of human response, ORENCIA should be used during pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers: Abatacept has been shown to be present in rat milk. It is not known whether abatacept is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ORENCIA, possibly including effects on the developing immune system, 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 ORENCIA in pediatric patients have not been established. **Geriatric Use:** A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA in clinical studies. No overall differences in safety or effectiveness were observed between these patients and younger patients, but these numbers are too low to rule out differences. The frequency of serious infection and malignancy among ORENCIA-treated patients 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 serious infections and malignancies (see **ADVERSE REACTIONS: Infections** and **ADVERSE REACTIONS: Malignancies**).

The most commonly reported adverse events (occurring in ≥10% of patients treated with ORENCIA) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

The adverse events most frequently resulting in clinical intervention (interruption or discontinuation of ORENCIA) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1.0%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

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.

The data described herein reflect exposure to ORENCIA (abatacept) in patients with active RA in placebo-controlled studies (1955 patients with ORENCIA, 989 with placebo). The studies had either a double-blind, placebo-controlled period of 6 months (258 patients with ORENCIA, 133 with placebo) or 1 year (1697 patients with ORENCIA, 856 with placebo). A subset of these patients received concomitant biologic DMARD therapy, such as a TNF blocking agent (204 patients with ORENCIA, 134 with placebo).

Infections: In the placebo-controlled trials, infections were reported in 54% of ORENCIA-treated patients and 48% of placebo-treated patients. The most commonly reported infections (reported in 5-13% of patients) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in fewer than 5% of patients at a higher frequency (>0.5%) with ORENCIA compared to placebo, were rhinitis, herpes simplex, and pneumonia (see **PRECAUTIONS: Infections**).

Serious infections were reported in 3.0% of patients treated with ORENCIA and 1.9% of patients treated with placebo. The most common (0.2-0.5%) serious infections reported with ORENCIA were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis (see **PRECAUTIONS: Infections**).

Malignancies: In the placebo-controlled portions of the clinical trials (1955 patients for a median of 12 months), the overall frequencies of malignancies were similar in the ORENCIA- and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in ORENCIA-treated patients (4, 0.2%) than placebo-treated patients (0). In the cumulative ORENCIA clinical trials (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the Surveillance, Epidemiology, and End Results Database.¹ Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers (see **PRECAUTIONS: Immunosuppression**). The potential role of ORENCIA in the development of malignancies in humans is unknown.

Infusion-Related Reactions and Hypersensitivity Reactions: Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion) in Studies III, IV, and V were more common in the ORENCIA-treated patients than the placebo patients (9% for ORENCIA, 6% for placebo). The most frequently reported events (1-2%) were dizziness, headache, and hypertension.

Acute infusion-related events that were reported in >0.1% and ≤1% of patients treated with ORENCIA included cardiopulmonary symptoms, such as hypotension, increased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild to moderate. Fewer than 1% of ORENCIA-treated patients discontinued due to an acute infusion-related event. In controlled trials, 6 ORENCIA-treated patients compared to 2 placebo-treated patients discontinued study treatment due to acute infusion-related events.

Of 2688 patients treated with ORENCIA in clinical trials, there were two cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients and generally occurred within 24 hours of ORENCIA infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction (see **PRECAUTIONS: Hypersensitivity**).

Adverse Reactions in Patients with COPD: In Study V, there were 37 patients with chronic obstructive pulmonary disease (COPD) who were treated with ORENCIA and 17 COPD patients who were treated with placebo. The COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in ORENCIA-treated patients compared to placebo-treated patients (43% vs 24%, respectively) including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of ORENCIA-treated patients developed a serious adverse event compared to placebo-treated patients (27% vs 6%), including COPD exacerbation (3 of 37 patients [8%] and pneumonia (1 of 37 patients [3%]).

Other Adverse Reactions: Adverse events occurring in 3% or more of patients and at least 1% more frequently in ORENCIA-treated patients during placebo-controlled RA studies are summarized in Table 1.

Table 1: Adverse Events Occurring in 3% or More of Patients and at Least 1% More Frequently in ORENCIA-Treated Patients During Placebo-Controlled RA Studies

Adverse Event (Preferred Term)	ORENCIA (n=1955) ^a Percentage	Placebo (n=989) ^b Percentage
Headache	18	13
Nasopharyngitis	12	9
Dizziness	9	7
Cough	8	7
Back pain	7	6
Hypertension	7	4
Dyspepsia	6	4
Urinary tract infection	6	5
Rash	4	3
Pain in extremity	3	2

^a Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).
^b Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

Immunogenicity: Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in RA patients for up to 2 years following repeated treatment with ORENCIA. Thirty-four of 1993 (1.7%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed. In this analysis it was observed that 9 of 154 (5.8%) patients that had discontinued treatment with ORENCIA for over 56 days developed antibodies.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies in a cell-based luciferase reporter assay. Six of 9 (67%) evaluable patients were shown to possess neutralizing antibodies.

No correlation of antibody development to clinical response or adverse events was observed. The data reflect the percentage of patients whose test results were positive for antibodies to abatacept in specific assays, and are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to abatacept with the incidence of antibodies to other products may be misleading.

OVERDOSAGE: ORENCIA is administered as an intravenous infusion under medically controlled conditions. Doses up to 50 mg/kg have been administered without apparent toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

DOSAGE AND ADMINISTRATION: See package insert for full prescribing information and instructions for reconstitution, dilution and dosage information.

REFERENCES: 1. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EF, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2001, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2001/. Accessed 2004.

 Bristol-Myers Squibb Company
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