

Stick With Antiresorptives, Even in Nonresponders

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SAN FRANCISCO — Antiresorptive therapy should be continued even in patients showing no apparent response, Dr. Douglas C. Bauer said at a meeting on osteoporosis sponsored by the University of California, San Francisco.

Monitoring response with periodic bone mineral density (BMD) testing may be misleading, said Dr. Bauer, of UCSF.

Furthermore, studies show that antiresorptive therapy decreases fracture risk even when BMD declines. And a patient whose BMD declines in the first year of therapy will often see an improvement in subsequent years.

Those advocating periodic monitoring cite several potential advantages of the practice, including increases in patient satisfaction, improvements in adherence, and the ability to change to more effective therapy in the presence of a nonresponse.

But Dr. Bauer pointed out that there are no studies demonstrating that monitoring improves patient satisfaction or adherence. Although it is true that many patients stop taking drugs to prevent osteoporosis, more than half of those who discontinue do so within 6 months of beginning therapy, he said. Measuring BMD 1-2 years following diagnosis is therefore unlikely to encourage adherence in the majority of patients.

In addition, changes in BMD on sub-

sequent measurements may be misleading. Although BMD is usually considered a very precise measurement, with precision errors in the neighborhood of 1%-2%, some apparent changes in BMD may be due to noise or to small differences in patient position, Dr. Bauer said.

To figure out what changes in BMD measurements are due to chance, Dr. Bauer recommended using the "least significant change" formula. The least significant change in any measurement is defined as three times the measurement's long-term reproducibility. For example, if a dual-energy x-ray absorptiometry instrument has a long-term coefficient of variation of 1.5%, then its least significant change would be 4.5%, meaning that changes of less than 4.5% from measurement to measurement may well be due to chance.

But even if a patient's BMD truly is declining, that does not necessarily mean that the patient is failing to respond to treatment, since he or she may well have lost more bone without treatment, he added.

And an initial loss of bone during treatment doesn't mean that this loss will continue. Dr. Bauer

quoted one study that showed that of patients who lost more than 4% of their BMD during the first year of treatment, 92% gained BMD in the second year, and the average increase during the second year was 4.8%. On the other hand, of patients who gained more than 8% in BMD during the first year, only 36% continue to gain BMD in the second year, and as a whole that group lost 1% of their BMD during that second-year.

An analysis of a clinical trial of alendronate versus placebo compared the patients who lost most BMD while taking alendronate with those who lost most BMD while taking placebo. Fracture risk was reduced by about 50% in those taking alendronate despite their loss of BMD.

Clinicians should consider secondary causes of osteoporosis in patients who are losing BMD despite antiresorptive therapy, Dr. Bauer said. Among the common secondary causes of bone loss are weight loss; medications such as corticosteroids, aromatase inhibitors, and gliptazones; inflammatory diseases or myeloma; or malabsorption.

"It's very useful to have these conversations [with patients] about follow-up measurements at the time you start therapy as opposed to having these conversations a year later or 2 years later," Dr. Bauer said.

"I always make a point ... to say that bone mineral density is a terrific test to decide who should be treated or who shouldn't be treated. But it's a lousy test to tell us whether you're benefiting from the therapy or not," he said.

clinical judgment of the health care professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be informed about the importance of regular testing of renal function and hematologic parameters when receiving treatment with ACTOplus met.

Therapy with a thiazolidinedione, which is the active pioglitazone component of the ACTOplus met tablet, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOplus met. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Combination antihyperglycemic therapy may cause hypoglycemia. When initiating ACTOplus met, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

Patients should be told to take ACTOplus met as prescribed and instructed that any change in dosing should only be done if directed by their physician.

Drug Interactions: Pioglitazone HCl

In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP450 isoform 3A4 substrate.

Drug Interactions: Metformin HCl

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of ACTOplus met and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving ACTOplus met, the patient should be closely observed to maintain adequate glycemic control.

Carcinogenesis, Mutagenesis, Impairment of Fertility

ACTOplus met
No animal studies have been conducted with ACTOplus met. The following data are based on findings in studies performed with pioglitazone or metformin individually.

Pioglitazone HCl

A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ. Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR α/γ activity; however, pioglitazone is a selective agonist for PPAR γ .

During prospective evaluation of urinary cytology involving more than 1800 patients receiving pioglitazone in clinical trials up to one year in duration, no new cases of bladder tumors were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with pioglitazone (0.72%) and patients treated with placebo (0.88%).

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPR1), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Metformin HCl

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times a human daily dose of 2000 mg of the metformin component of ACTOplus met based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no

tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose of the metformin component of ACTOplus met based on body surface area comparisons.

Animal Toxicology

Pioglitazone HCl

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with the pioglitazone HCl component of ACTOplus met (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy: Pregnancy Category C

ACTOplus met

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. ACTOplus met should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

There are no adequate and well-controlled studies in pregnant women with ACTOplus met or its individual components. No animal studies have been conducted with the combined products in ACTOplus met. The following data are based on findings in studies performed with pioglitazone or metformin individually.

Pioglitazone HCl

Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2 , respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

Metformin HCl

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times a human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

No studies have been conducted with the combined components of ACTOplus met. In studies performed with the individual components, both pioglitazone and metformin are secreted in the milk of lactating rats. It is not known whether pioglitazone and/or metformin is secreted in human milk. Because many drugs are excreted in human milk, ACTOplus met should not be administered to a breastfeeding woman. If ACTOplus met is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

Safety and effectiveness of ACTOplus met in pediatric patients have not been established.

Elderly Use

Pioglitazone HCl: Approximately 500 patients in placebo-controlled clinical trials of pioglitazone were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

Metformin HCl:

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, ACTOplus met should only be used in patients with normal renal function (see **CONTRAINDICATIONS** and **WARNINGS**). Because aging is associated with reduced renal function, ACTOplus met should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of ACTOplus met (see **WARNINGS**).

ADVERSE REACTIONS

The most common adverse events reported in at least 5% of patients in the controlled 16-week clinical trial between placebo plus metformin and pioglitazone 30 mg plus metformin were upper respiratory tract infection (15.6% and 15.5%), diarrhea (6.3% and 4.8%), combined edema/peripheral edema (2.5% and 6.0%) and headache (1.9% and 6.0%), respectively. The incidence and type of adverse events reported in at least 5% of patients in any combined treatment group from the 24-week study comparing pioglitazone 30 mg plus metformin and pioglitazone 45 mg plus metformin are shown in Table 2; the rate of adverse events resulting in study discontinuation between the two treatment groups was 7.8% and 7.7%, respectively.

Table 2. Adverse Events That Occurred in $\geq 5\%$ of Patients in Any Treatment Group During the 24-Week Study

Adverse Event Preferred Term	Pioglitazone 30 mg + metformin N=411 n (%)	Pioglitazone 45 mg + metformin N=416 n (%)
Upper Respiratory Tract Infection	51 (12.4)	56 (13.5)
Diarrhea	24 (5.8)	20 (4.8)
Nausea	24 (5.8)	15 (3.6)
Headache	19 (4.6)	22 (5.3)
Urinary Tract Infection	24 (5.8)	22 (5.3)
Sinusitis	18 (4.4)	21 (5.0)
Dizziness	22 (5.4)	20 (4.8)
Edema Lower Limb	12 (2.9)	47 (11.3)
Weight Increased	12 (2.9)	28 (6.7)

Most clinical adverse events were similar between groups treated with pioglitazone in combination with metformin and those treated with pioglitazone monotherapy. Other adverse events reported in at least 5% of patients in controlled clinical trials between placebo and pioglitazone monotherapy included myalgia (2.7% and 5.4%), tooth disorder (2.3% and 5.3%), diabetes mellitus aggravated (8.1% and 5.1%) and pharyngitis (0.8% and 5.1%), respectively.

In U.S. double-blind studies, anemia was reported in $\leq 2\%$ of patients treated with pioglitazone plus metformin (see **PRECAUTIONS** section).

In monotherapy studies, edema was reported for 4.8% of patients treated with pioglitazone versus 1.2% of placebo-treated patients. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS** section).

Laboratory Abnormalities

Hematologic: Pioglitazone may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with pioglitazone appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with pioglitazone. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with pioglitazone therapy and have rarely been associated with any significant hematologic clinical effects (see **PRECAUTIONS** section).

In controlled clinical trials of metformin at 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation (see **PRECAUTIONS** section).

Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with pioglitazone had ALT values ≥ 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with pioglitazone, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with pioglitazone were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see **PRECAUTIONS** section).

CPK Levels: During required laboratory testing in clinical trials with pioglitazone, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). Six of these patients continued to receive pioglitazone, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone therapy is unknown.

OVERDOSAGE

Pioglitazone HCl

During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

Metformin HCl

Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin HCl has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **WARNINGS**). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated metformin from patients in whom metformin overdosage is suspected.

INDICATIONS: ACTOplus met is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.

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Manufactured by:
Takeda Pharmaceutical Company Limited
Osaka, JAPAN

Marketed by:
Takeda Pharmaceuticals America, Inc.
475 Half Day Road
Lincolnshire, IL 60069

05-1115 Revised: August, 2005

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L-PIOM-00105