

# Posttransplant HCV Prophylaxis Shows Promise

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BOSTON — Prophylaxis with pegylated interferon plus ribavirin is relatively safe and well tolerated following liver transplantation for hepatitis C, a study has shown.

Preliminary findings from the first randomized control trial of antiviral prophylaxis for the prevention of recurrent hepatitis C infection in orthotopic liver-transplant (OLT) patients suggest

that although adverse events are common during prophylactic treatment with peg-interferon  $\alpha$ -2a (Pegasys) plus ribavirin (Copegus), only a small percentage of those adverse events necessitate treatment withdrawal, Dr. Natalie H. Bzowej said at the annual meeting of the American Association for the Study of Liver Diseases.

Because recurrent infection with the hepatitis C virus (HCV) can cause graft failure and death following liver transplantation, preemptive antiviral therapy has been

suggested as a way to enhance viral clearance. However, safety concerns—particularly regarding anemia, neutropenia, and acute cellular rejection—have limited its use, said Dr. Bzowej of California Pacific Medical Center in San Francisco.

To assess the safety and efficacy of preemptive antiviral therapy following liver transplant and to compare the outcomes of patients undergoing prophylactic treatment to those of patients who don't receive treatment until recurrent hepatitis

has become established in the graft, Dr. Bzowej and her colleagues in the ongoing Phoenix study out of the Mayo Clinic to date have randomized 115 post-liver transplant patients to either a prophylaxis or an observation arm. Dr. Bzowej presented data on the first 60 randomized patients.

Of the 60 patients, 33 were randomized to prophylaxis with 135 mcg peginterferon  $\alpha$ -2a per week for 4 weeks, followed by 180 mcg/week for 44 weeks, plus ribavirin, at an initial dosage of 400 mg/day, escalating to 1,000 mg or 1,200 mg/day over the first 12 weeks, for 48 weeks. The 27 patients randomized to observation received no treatment until histologic recurrence of HCV, Dr. Bzowej reported.

All of the patients in the study were randomized 10-26 weeks post transplant. Previous investigations into preemptive therapy have begun prophylaxis as early as 4 weeks post transplant, "but doing so excludes a number of potential candidates who are still recovering from surgery," Dr. Bzowej said.

After randomization and before treatment initiation, one patient in the prophylaxis arm and three patients in the observation arm withdrew consent for the study. Of the 32 patients who began treatment in the prophylaxis arm, 7 withdrew. Four of the patients in the observation arm crossed over to treatment because of HCV recurrence.

During the first 12 study weeks, 94% of the prophylaxis arm and 82% of the observation arm experienced one or more adverse events, with a total of 278 and 107 adverse events, respectively. Additionally, 19% of patients in the prophylaxis arm and 15% in the observation arm experienced one or more serious adverse events, with a total of seven and six serious adverse events, respectively.

"The most common treatment-related adverse events were fatigue, anemia, headache, and nausea," Dr. Bzowej said.

With respect to treatment modifications or interruptions, of the 32 patients assigned to the prophylaxis arm, 6 (19%) withdrew from therapy because of adverse events. Five of the six withdrew from both pegylated interferon  $\alpha$ -2a and ribavirin—one for rash and anemia, one for thrombocytopenia, one for increased bilirubin, one for dehydration, and one for neutropenia. The sixth patient withdrew from the ribavirin only because of anemia. None of the four crossover patients in the observation arm withdrew from treatment.

Importantly, "no clinically apparent episodes of acute cellular rejection occurred through week 12," Dr. Bzowej said. And although adverse events occurred in 94% of the prophylactically treated patients, "only 19% experienced events necessitating therapeutic withdrawal—a figure that compares favorably with other studies, suggesting the regimen is reasonably well tolerated," she said.

Dr. Bzowej disclosed that she has been a speaker for Schering and Glaxo and that she has served as a consultant for Intarcia. She has also been an investigator on clinical trials supported by numerous companies, including Roche Laboratories, which manufactures Pegasys. ■

ment of the health care professional (see **PRECAUTIONS, General: Pioglitazone hydrochloride** and **ADVERSE REACTIONS, Serum Transaminase Levels**).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B<sub>12</sub> deficiency should be excluded.

#### Information for Patients

Patients should be instructed regarding the importance of adhering to dietary instructions, a regular exercise program, and regular testing of blood glucose and A1C. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

The risks of lactic acidosis, its symptoms and conditions that predispose to its development, as noted in the **WARNINGS, Metformin hydrochloride** and **PRECAUTIONS, General: Metformin hydrochloride** sections, should be explained to patients. Patients should be advised to discontinue ACTOPLUS MET immediately and to promptly notify their health care professional if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Gastrointestinal symptoms are common during initiation of metformin treatment and may occur during initiation of ACTOPLUS MET therapy; however, patients should consult with their physician if they develop unexplained symptoms. Although gastrointestinal symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to lactic acidosis or other serious disease.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving ACTOPLUS MET.

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on ACTOPLUS MET should immediately report these symptoms to their physician.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy and periodically thereafter per the 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 TZD, 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 hydrochloride

*In vivo* drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP450 isozyme 3A4 substrate. An enzyme inhibitor of CYP2C8 (such as gemfibrozil) may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 (such as rifampin) may significantly decrease the AUC of pioglitazone. Therefore, if an inhibitor or inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response.

##### Metformin hydrochloride

**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<sub>max</sub> by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C<sub>max</sub> 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<sub>max</sub> and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T<sub>max</sub> 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 hypoglycemia 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.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is therefore less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol and probenecid.

#### 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 hydrochloride

A two-year carcinogenicity study was conducted in male and female rats at oral doses  $\leq 63$  mg/kg (~14x the maximum recommended human oral dose of 45 mg based on mg/m<sup>2</sup>). 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  $\geq 4$  mg/kg/day (~ the maximum rec-

ommended human oral dose based on mg/m<sup>2</sup>). A two-year carcinogenicity study was conducted in male and female mice at oral doses  $\leq 100$  mg/kg/day (~11x the maximum recommended human oral dose based on mg/m<sup>2</sup>). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving >1800 patients receiving pioglitazone in clinical trials  $\leq$  one year in duration, no new cases of bladder tumors were identified. In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was < one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone and two (0.05%) on placebo.

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/XPRT), 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  $\leq 40$  mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (~9x the maximum recommended human oral dose based on mg/m<sup>2</sup>).

**Metformin hydrochloride**  
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses  $\leq 900$  mg/kg/day and 1500 mg/kg/day, respectively. These doses are both ~4x 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 ~3x the maximum recommended human daily dose of the metformin component of ACTOPLUS MET based on body surface area comparisons.

#### Animal Toxicology

##### Pioglitazone hydrochloride

Heart enlargement has been observed in mice (100 mg/kg), rats ( $\geq 4$  mg/kg) and dogs (3 mg/kg) treated orally with the pioglitazone HCl component of ACTOPLUS MET (~11, 1, and 2x the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m<sup>2</sup>). 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 (~35x the maximum recommended human oral dose based on mg/m<sup>2</sup>). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (~4x the maximum recommended human oral dose based on mg/m<sup>2</sup>), but not in a 52-week study at oral doses up to 32 mg/kg (~13x the maximum recommended human oral dose based on mg/m<sup>2</sup>).

##### 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 hydrochloride

Pioglitazone was not teratogenic in rats at oral doses  $\leq 80$  mg/kg or in rabbits given  $\leq 160$  mg/kg during organogenesis (~17 and 40x the maximum recommended human oral dose based on mg/m<sup>2</sup>, 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  $\geq 40$  mg/kg/day (~10x the maximum recommended human oral dose based on mg/m<sup>2</sup>). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (~40x the maximum recommended human oral dose based on mg/m<sup>2</sup>). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of  $\geq 10$  mg/kg during late gestation and lactation periods (~2x the maximum recommended human oral dose based on mg/m<sup>2</sup>).

##### Metformin hydrochloride

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 hydrochloride  
~500 patients in placebo-controlled clinical trials of pioglitazone were  $\geq 65$ . No significant differences in effectiveness and safety were observed between these patients and younger patients.

##### Metformin hydrochloride

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, WARNINGS, Metformin hydrochloride**). 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, Metformin hydrochloride**).

#### ADVERSE REACTIONS

The most common adverse events reported in  $\geq 5\%$  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  $\geq 5\%$  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  $\geq 5\%$  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, General: Pioglitazone hydrochloride**). In monotherapy studies, edema was reported for 4.8% (with doses from 7.5 mg to 45 mg) of patients treated with pioglitazone vs 1.2% of placebo-treated patients. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS, General: Pioglitazone hydrochloride**). Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see **PRECAUTIONS, General: Pioglitazone hydrochloride**).

#### 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%-4% in patients treated with pioglitazone. These changes generally occurred within the first 4-12 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, General: Pioglitazone hydrochloride**).

In controlled clinical trials of metformin at 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in ~7% of patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B<sub>12</sub> supplementation (see **PRECAUTIONS, General: Metformin hydrochloride**).

**Serum Transaminase Levels:** During all clinical studies in the U.S., 14/4780 (0.30%) patients treated with pioglitazone had ALT values  $\geq 3$ x the ULN 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, General: Pioglitazone hydrochloride**).

**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  $>10$ x the ULN was noted in 9 patients (values of 2150-11400 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 hydrochloride

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 overdose, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

##### Metformin hydrochloride

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

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Manufactured by:  
**Takeda Pharmaceutical Company Limited**  
Osaka, JAPAN

Marketed by:  
**Takeda Pharmaceuticals America, Inc.**  
One Takeda Parkway  
Deerfield, IL 60015

05-1134, November 2006

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L-PIOM-00015