

Genes Plus Family History Show Prostate Ca Risk

BY BRUCE JANCIN

DENVER — A man's absolute risk of developing prostate cancer over a 20-year period can be estimated by determining the number of risk alleles present on a simple genetic test and then taking family history into account.

It's known that an average 55-year-old man has a 13% risk of developing prostate cancer during the next 20 years.

But by adding up how many of 14 known risk alleles the man has on single-nucleotide polymorphisms, his risk can be defined far more accurately.

For example, a man with seven or fewer of the risk alleles plus a negative family history has only an 8% absolute risk of being diagnosed with prostate cancer at age 55-74. The risk shoots up to 52% in a man with 14 risk alleles and a positive family history, Dr. Jianfeng Xu explained

at the annual meeting of the American Association for Cancer Research.

This latter highest-risk group includes 8% of the general adult male population, noted Dr. Xu, professor of epidemiology and cancer biology at Wake Forest University, Winston-Salem, N.C.

He and his coworkers developed their risk model by studying 2,893 men with prostate cancer and 1,781 without the disease who had previously participated

in a Swedish case-control study. The investigators found that while each of the risk alleles contributed a relatively small increase in risk, the risk was additive.

Moreover, the risk was further enhanced in a predictable way by the presence of a positive family history. For example, the 20-year absolute risk in a man with seven or fewer risk alleles and a negative family history is a mere 8%, but it rises to 17% with a positive family history. At the other extreme, a man possessing 14 risk alleles but a negative family history has a 24% risk of being diagnosed with prostate cancer at age 55-



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DR. XU

74; having a positive family history increases that risk to 52%.

The investigators subsequently confirmed their findings in a retrospective analysis of data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Dr. Xu conceded that the model has a major limitation: It doesn't distinguish between indolent and aggressive forms of prostate cancer. Thus, using the model would likely result in overtreatment of many men identified as being at high absolute risk, but who have indolent disease. The investigators have identified several single-nucleotide polymorphisms that appear to distinguish between nonaggressive and lethal prostate cancer, however, and are now doing confirmatory testing.

Even if these new candidate risk alleles don't pan out, Dr. Xu said he sees the current version of the absolute risk assessment as having potential utility. For example, men identified as high risk might elect to embark on a program of risk reduction through diet and lifestyle modification along with chemoprevention using finasteride, which has been shown to reduce prostate cancer risk by about 25%.

For men at average risk, finasteride could reduce their 20-year absolute risk from 13% to 10% at the cost of roughly \$1.6 million per life-year gained. But for men at very high risk, the absolute risk reduction conferred by finasteride would be substantially greater and cost per life-year gained would be lower, Dr. Xu said.

He and his colleagues plan to launch a prospective prostate cancer prevention trial using risk alleles and family history to guide chemoprevention with finasteride.

"More replication is definitely needed before this is ready to go to the clinic, but this is taking us one step closer to the personalized medicine approach," observed Dr. Peter G. Shields of the department of medicine at Georgetown University Medical Center and deputy director of the Lombardi Comprehensive Cancer Center, Washington.

TOVIAZ™ (fesoterodine fumarate) extended release tablets

R_x only

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE

Toviaz is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

Toviaz is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Toviaz is also contraindicated in patients with known hypersensitivity to the drug or its ingredients.

PRECAUTIONS

General

Bladder Outlet Obstruction: Toviaz should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention (see CONTRAINDICATIONS).

Decreased Gastrointestinal Motility: Toviaz, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation.

Controlled Narrow-Angle Glaucoma: Toviaz should be used with caution in patients being treated for narrow-angle glaucoma, and only where the potential benefits outweigh the risks (see CONTRAINDICATIONS).

Reduced Hepatic Function: There are no dosing adjustments for patients with mild or moderate hepatic impairment. Toviaz has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations in full prescribing information and DOSAGE AND ADMINISTRATION).

Myasthenia Gravis: Toviaz should be used with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

Reduced Renal Function: There are no dosing adjustments for patients with mild or moderate renal insufficiency. Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal insufficiency (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations in full prescribing information and DOSAGE AND ADMINISTRATION).

Concomitant Administration with CYP3A4 Inhibitors: Doses of Toviaz greater than 4 mg are not recommended in patients taking a potent CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin).

In patients taking weak or moderate CYP3A4 inhibitors (e.g. erythromycin), careful assessment of tolerability at the 4 mg daily dose is advised prior to increasing the daily dose to 8 mg. While this specific interaction potential was not examined by clinical study, some pharmacokinetic interaction is expected, albeit less than that observed with potent CYP3A4 inhibitors (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions in full prescribing information and DOSAGE AND ADMINISTRATION).

Information for Patients

Patients should be informed that Toviaz, like other antimuscarinic agents, may produce clinically significant adverse effects related to antimuscarinic pharmacological activity including constipation and urinary retention. Toviaz, like other antimuscarinics, may be associated with blurred vision, therefore, patients should be advised to exercise caution until the drug's effects on the patient have been determined. Heat prostration (due to decreased sweating) can occur when Toviaz, like other antimuscarinic drugs, is used in a hot environment. Patients should also be informed that alcohol may enhance the drowsiness caused by Toviaz, like other anticholinergic agents. Patients should read the patient leaflet entitled "Patient Information TOVIAZ™" before starting therapy with Toviaz.

Drug Interactions

Coadministration of Toviaz with other antimuscarinic agents that produce dry mouth, constipation, urinary retention, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Also see PRECAUTIONS, Concomitant Administration with CYP3A4 Inhibitors.

Drug-Laboratory Test Interactions

Interactions between Toviaz and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of drug-related carcinogenicity was found in 24-month studies with oral administration to mice and rats. The highest tolerated doses in mice (females 45 to 60 mg/kg/day, males 30 to 45 mg/kg/day) correspond to 11- to 19-fold (females) and 4- to 9-fold (males) the estimated human AUC values reached with fesoterodine 8 mg, which is the Maximum Recommended Human Dose (MRHD). In rats, the highest tolerated dose (45 to 60 mg/kg/day) corresponds to 3- to 8-fold (females) and 3- to 14-fold (males), the estimated human AUC at the MRHD.

Fesoterodine was not mutagenic or genotoxic in vitro (Ames tests, chromosome aberration tests) or in vivo (mouse micronucleus test).

Fesoterodine had no effect on reproductive function, fertility, or early embryonic development of the fetus at non-maternally toxic doses in mice. The maternal No-Observed-Effect Level (NOEL) and the NOEL for effects on reproduction and early embryonic development were both 15 mg/kg/day. Based on AUC, the systemic exposure was 0.6- to 1.5-fold higher in mice than in humans at the MRHD, whereas based on peak plasma concentrations, the exposure in mice was 5- to 9-fold higher. The Lowest-Observed-Effect Level (LOEL) for maternal toxicity was 45 mg/kg/day.

Pregnancy

Pregnancy Category C

Reproduction studies have been performed in mice and rabbits. No dose-related teratogenicity was observed at oral doses up to 75 mg/kg/day in mice (6 to 27 times the expected exposure at the MRHD based on AUC and greater than 77 times the expected C_{max}) and up to 27 mg/kg/day in rabbits (3- to 11-fold by AUC and 19- to 62-fold by C_{max}) or at subcutaneous doses up to 4.5 mg/kg/day in rabbits (9- to 11-fold by AUC and 43- to 56-fold by C_{max}). In mice treated orally with 75 mg/kg/day (6- to 27-times the expected exposure at the MRHD based on AUC and greater than 77-times the expected C_{max}), increased resorptions and decreased live fetuses were observed. One fetus with cleft palate was observed at each dose (15, 45 and 75 mg/kg/day), at an incidence within the background historical range. In rabbits treated orally with 27 mg/kg/day (3- to 11-fold by AUC and 19- to 62-fold by C_{max}), incompletely ossified sternebrae (retardation of bone development) were observed in fetuses. In rabbits treated by subcutaneous (sc) administration with 4.5 mg/kg/day (9- to 11-fold by AUC and 43- to 53-fold by C_{max}), maternal toxicity and incompletely ossified sternebrae were observed in fetuses (at an incidence within the background historical range). At 1.5 mg/kg/day s.c., (3-fold by AUC and 11- to 13-fold by C_{max}), decreased maternal food consumption in the absence of any fetal effects was observed. Oral administration of 30 mg/kg/day fesoterodine to mice in a pre- and post-natal development study resulted in decreased body weight of the dams and delayed ear opening of the pups. No effects were noted on mating and reproduction of the F₁ dams or on the F₂ offspring.

There are no adequate and well-controlled studies using Toviaz in pregnant women. Therefore, Toviaz should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers

It is not known whether fesoterodine is excreted in human milk. Toviaz should not be administered during nursing unless the potential benefit outweighs the potential risk to the neonate.

Pediatric Use

The safety and effectiveness of Toviaz in pediatric patients have not been established.

Geriatric Use

Of 1567 patients who received Toviaz 4 mg/day or 8 mg/day in the Phase 2 and 3, placebo-controlled, efficacy and safety studies, 515 (33%) were 65 years of age or older, and 140 (9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies; however, the incidence of antimuscarinic adverse events, including dry mouth, constipation, dyspepsia, increase in residual urine, dizziness (at 8 mg only) and urinary tract infection, was higher in patients 75 years of age and older as compared to younger patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and CLINICAL STUDIES in full prescribing information and ADVERSE REACTIONS).

ADVERSE REACTIONS

The safety of Toviaz was evaluated in Phase 2 and 3 controlled trials in a total of 2859 patients with overactive bladder of which 2288 were treated with fesoterodine. Of this total, 782 received Toviaz 4 mg/day, and 785 received Toviaz 8 mg/day in Phase 2 or 3 studies with treatment periods of 8 or 12 weeks. Approximately 80% of these patients had >10 weeks exposure to Toviaz in these trials.

A total of 1964 patients participated in two 12-week, Phase 3 efficacy and safety studies and subsequent open-label extension studies. In these 2 studies combined, 554 patients received Toviaz 4 mg/day and 566 patients received Toviaz 8 mg/day.

In Phase 2 and 3 placebo-controlled trials combined, the incidences of serious adverse events in patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg were 1.9%, 3.5%, and 2.9%, respectively. All serious adverse events were judged to be not related or unlikely to be related to study medication by the investigator, except for four patients receiving Toviaz who reported one serious adverse event each: angina, chest pain, gastroenteritis, and QT prolongation on ECG.

The most commonly reported adverse event in patients treated with Toviaz was dry mouth. The incidence of dry mouth was higher in those taking 8 mg/day (35%) and in those taking 4 mg/day (19%), as compared to placebo (7%). Dry mouth led to discontinuation in 0.4%, 0.4%, and 0.8% of patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg, respectively. For those patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

The second most commonly reported adverse event was constipation. The incidence of constipation was 2% in those taking placebo, 4% in those taking 4 mg/day, and 6% in those taking 8 mg.

Table 3 lists adverse events, regardless of causality, that were reported in the combined Phase 3, randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with Toviaz 4 mg or 8 mg once daily for up to 12 weeks.

Table 3. Adverse events with an incidence exceeding the placebo rate and reported by ≥1% of patients from double-blind, placebo-controlled Phase 3 trials of 12 weeks' treatment duration

System organ class	Preferred term	Placebo N=554 %	Toviaz 4 mg/day N=554 %	Toviaz 8 mg/day N=566 %
Gastrointestinal disorders	Dry mouth	7.0	18.8	34.6
	Constipation	2.0	4.2	6.0
	Dyspepsia	0.5	1.6	2.3
	Nausea	1.3	0.7	1.9
	Abdominal pain upper	0.5	1.1	0.5
Infections	Urinary tract infection	3.1	3.2	4.2
	Upper respiratory tract infection	2.2	2.5	1.8
Eye disorders	Dry eyes	0	1.4	3.7
Renal and urinary disorders	Dysuria	0.7	1.3	1.6
	Urinary retention	0.2	1.1	1.4
Respiratory disorders	Cough	0.5	1.6	0.9
	Dry throat	0.4	0.9	2.3
General disorders	Edema peripheral	0.7	0.7	1.2
Musculoskeletal disorders	Back pain	0.4	2.0	0.9
Psychiatric disorders	Insomnia	0.5	1.3	0.4
Investigations	ALT increased	0.9	0.5	1.2
	GGT increased	0.4	0.4	1.2
Skin disorders	Rash	0.5	0.7	1.1

ALT=alanine aminotransferase, GGT=gamma glutamyltransferase

Patients also received Toviaz for up to three years in open-label extension phases of one Phase 2 and two Phase 3 controlled trials. In all open-label trials combined, 857, 701, 529, and 105 patients received Toviaz for at least 6 months, 1 year, 2 years, and 3 years respectively. The adverse events observed during long-term, open-label studies were similar to those observed in the 12-week, placebo-controlled studies, and included dry mouth, constipation, dry eyes, dyspepsia and abdominal pain. Similar to the controlled studies, most adverse events of dry mouth and constipation were mild to moderate in intensity. Serious adverse events, judged to be at least possibly related to study medication by the investigator, and reported more than once during the open-label treatment period of up to 3 years included urinary retention (3 cases), diverticulitis (3 cases), constipation (2 cases), irritable bowel syndrome (2 cases), and electrocardiogram QT corrected interval prolongation (2 cases).

OVERDOSAGE

Overdosage with Toviaz can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended.

DOSAGE AND ADMINISTRATION

The recommended starting dose of Toviaz is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily.

The daily dose of Toviaz should not exceed 4 mg in the following populations:

- Patients with severe renal insufficiency (CL_{cr} <30 mL/min).
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin.

Toviaz is not recommended for use in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations in full prescribing information and PRECAUTIONS).

Toviaz should be taken with liquid and swallowed whole. Toviaz can be administered with or without food, and should not be chewed, divided, or crushed.

Manufactured by:

SCHWARZ PHARMA PRODUKTIONS-GmbH, 08056 Zwickau, Germany

Distributed by: Pfizer Labs, Division of Pfizer Inc, NY, NY 10017

LAB-0381-3.0

Revised November 2008

