

MRI Detects More Breast Ca in High-Risk Women

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Chicago Bureau

CHICAGO — Magnetic resonance imaging detects more breast cancers in high-risk women, compared with mammography or ultrasound, according to two studies presented at the annual meeting of the Radiological Society of North America.

MRI was more sensitive but less specific in the detection of breast cancer than

was mammography or ultrasound, data from the Austrian Screening Trial show. However, the lesser specificity of MRI was partially caused by a higher detection rate for atypical ductal hyperplasias, which are considered to be direct precursors of invasive ductal cancer, said Dr. Christopher Riedl of the Medical University of Vienna.

In the second study, screening MRI was associated with a higher biopsy rate, but was the only modality that detected all

cancers identified in the study, conducted by the International Breast MRI Consortium and the Cancer Genetics Network. Findings of the prospective multicenter trial support single-site studies that show MRI has greater sensitivity and cancer yield than any other screening modality in high-risk populations, said Dr. Constance Lehman of the University of Washington in Seattle.

Dr. Lehman and associates performed screening mammography, MRI, and ul-

trasound within 90 days of each other in 171 asymptomatic women aged 25 years or older who had a known breast cancer susceptibility gene (BRCA) mutation or who were at a 20% or greater lifetime risk of breast cancer.

Sixteen biopsies were performed and six cancers were detected for an overall 3.5% diagnostic yield.

MRI detected all six cancers, while mammography detected two, and ultrasound detected one. The diagnostic yields for each test were: MRI 3.5%, mammography 1.2%, and ultrasound 0.6%, the investigators reported.

All six cancers were infiltrating ductal carcinoma. The one cancer detected by all three modalities was a stage T2/N1/M0 cancer.

MRI resulted in the highest rate of biopsies being performed (8.2% of women) compared with mammography (2.3%) and ultrasound (2.3%), she said.

Nine biopsies were performed on women whose only positive exam was an MRI. Cancer was diagnosed in four of those women, meaning that the risk of a benign biopsy based on an MRI-only positive exam was 2.9% (five of nine biopsies). Another way to interpret this finding is that, "if we screened a thousand high-risk women, adding MRI to mammography would add 29 additional benign biopsies with 30 additional invasive cancers predicted to be detected," Dr. Lehman said.

The Austrian Screening Trial evaluated 327 women with a BRCA mutation or strong family history for breast cancer using annual MRI, mammography, and ultrasound screening between days 8 and 12 of their menstrual cycle to decrease false-positive rates due to hormonal influences. The women, aged 22-80 years (mean 41 years), underwent a total of 672 complete imaging rounds.

A total of 28 cancers were found, of which 39% were ductal carcinoma in situ (DCIS) and 61% were invasive cancers, Dr. Riedl and colleagues reported.

Of the 28 cancers, MRI detected 24, mammography 14, and ultrasound 12. Sensitivity was significantly higher for MRI (86%) than for mammography (50%) or ultrasound (43%). Almost one-half of the cancers (43%) were detected only by MRI. Of the 11 DCIS cases, MRI detected 10, mammography 5, and ultrasound 4. Five of the DCIS lesions were detected by MRI only.

MRI, mammography, and ultrasound led to 101, 25, and 26 false-positive findings, respectively, resulting in a significantly worse specificity for MRI (81%) than mammography (64%) or ultrasound (68%).

Of the total 108 false-positive findings, 39 were diagnosed as atypical ductal hyperplasia. Significantly more cases were detected by MRI (36) than by mammography (10) or ultrasound (4). Twenty-five cases were found by MRI only.

A growing body of evidence suggests that atypical ductal hyperplasia is a genetically advanced precancerous lesion, and that, similar to DCIS, it is a nonobligatory, direct precursor of invasive ductal cancer, Dr. Riedl said.

Famvir® (famciclovir)

Tablets

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Herpes Zoster: Famvir® (famciclovir) is indicated for the treatment of acute herpes zoster (shingles).

Herpes Simplex Infections: Famvir is indicated for:

- treatment or suppression of recurrent genital herpes in immunocompetent patients.
- treatment of recurrent herpes labialis (cold sores) in immunocompetent patients.
- treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients.

CONTRAINDICATIONS

Famvir® (famciclovir) is contraindicated in patients with known hypersensitivity to the product, its components, and Denavir® (penciclovir cream).

PRECAUTIONS

General

The efficacy of Famvir® (famciclovir) has not been established for initial episode genital herpes infection, ophthalmic zoster, disseminated zoster or in immunocompromised patients with herpes zoster.

Dosage adjustment is recommended when administering Famvir to patients with creatinine clearance values <60 mL/min. (see DOSAGE AND ADMINISTRATION in the full prescribing information). In patients with underlying renal disease who have received inappropriately high doses of Famvir for their level of renal function, acute renal failure has been reported.

Famvir 125 mg, 250 mg and 500 mg tablets contain lactose (26.9 mg, 53.7 mg and 107.4 mg, respectively). Patients with rare hereditary problems of galactose intolerance, a severe lactase deficiency or glucose-galactose malabsorption should not take Famvir 125 mg, 250 mg and 500 mg tablets.

Information for Patients

Patients should be informed that Famvir is not a cure for genital herpes. There are no data evaluating whether Famvir will prevent transmission of infection to others. As genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of recurrent episodes is indicated, patients should be advised to initiate therapy at the first sign or symptom.

There is no evidence that Famvir will affect the ability of a patient to drive or to use machines. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking Famvir should refrain from driving or operating machinery.

Drug Interactions

Concurrent use with probenecid or other drugs significantly eliminated by active renal tubular secretion may result in increased plasma concentrations of penciclovir.

The conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme could potentially occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Famciclovir was administered orally unless otherwise stated.

Carcinogenesis: Two-year dietary carcinogenicity studies with famciclovir were conducted in rats and mice. An increase in the incidence of mammary adenocarcinoma (a common tumor in animals of this strain) was seen in female rats receiving the high dose of 600 mg/kg/day (1.1 to 4.5x the human systemic exposure at the recommended total daily oral dose ranging between 2000 mg and 5000 mg, based on area under the plasma concentration curve comparisons [24 hr AUC] for penciclovir). No increases in tumor incidence were reported in male rats treated at doses up to 240 mg/kg/day (0.7 to 2.7x the human AUC), or in male and female mice at doses up to 600 mg/kg/day (0.3 to 1.2x the human AUC).

Mutagenesis: Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a battery of *in vitro* and *in vivo* assays. Famciclovir and penciclovir were negative in *in vitro* tests for gene mutations in bacteria (*S. typhimurium* and *E. coli*) and unscheduled DNA synthesis in mammalian HeLa 83 cells (at doses up to 10,000 and 5,000 mcg/plate, respectively). Famciclovir was also negative in the L5178Y mouse lymphoma assay (5000 mcg/mL), the *in vivo* mouse micronucleus test (4800 mg/kg), and rat dominant lethal study (5000 mg/kg). Famciclovir induced increases in polyploidy in human lymphocytes *in vitro* in the absence of chromosomal damage (1200 mcg/mL). Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutation/chromosomal aberrations, with and without metabolic activation (1000 mcg/mL). In human lymphocytes, penciclovir caused chromosomal aberrations in the absence of metabolic activation (250 mcg/mL). Penciclovir caused an increased incidence of micronuclei in mouse bone marrow *in vivo* when administered intravenously at doses highly toxic to bone marrow (500 mg/kg), but not when administered orally.

Impairment of Fertility: Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of the seminiferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of toxicity to male reproduction was related to dose and duration of exposure. In male rats, decreased fertility was observed after 10 weeks of dosing at 500 mg/kg/day (1.4 to 5.7x the human AUC). The no observable effect level for sperm and testicular toxicity in rats following chronic administration (26 weeks) was 50 mg/kg/day (0.15 to 0.6x the human systemic exposure based on AUC comparisons). Testicular toxicity was observed following chronic administration to mice (104 weeks) and dogs (26 weeks) at doses of 600 mg/kg/day (0.3 to 1.2x the human AUC) and 150 mg/kg/day (1.3 to 5.1x the human AUC), respectively.

Famciclovir had no effect on general reproductive performance or fertility in female rats at doses up to 1000 mg/kg/day (2.7 to 10.8x the human AUC).

Two placebo-controlled studies in a total of 130 otherwise healthy men with a normal sperm profile over an 8-week baseline period and recurrent genital herpes receiving oral Famvir (250 mg b.i.d.) (n=66) or placebo (n=64) therapy for 18 weeks showed no evidence of significant effects on sperm count, motility or morphology during treatment or during an 8 week follow-up.

Teratology

Pregnancy Effects—Pregnancy Category B: Famciclovir was tested for effects on embryo-fetal development in rats and rabbits at oral doses up to 1000 mg/kg/day (approximately 2.7 to 10.8x and 1.4 to 5.4x the human systemic exposure to penciclovir based on AUC comparisons for the rat and rabbit, respectively) and intravenous doses of 360 mg/kg/day in rats (1.5 to 6x the human dose based on body surface area [BSA] comparisons) or 120 mg/kg/day in rabbits (1.1 to 4.5x the human dose [BSA]). No adverse effects were observed on embryo-fetal development. Similarly, no adverse effects were observed following intravenous administration of penciclovir to rats (80 mg/kg/day, 0.3 to 1.3x the human dose [BSA]) or rabbits (60 mg/kg/day, 0.5 to 2.1x the human dose [BSA]). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, famciclovir should be used during pregnancy only if the benefit to the patient clearly exceeds the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to Famvir, Novartis Pharmaceuticals Corporation maintains a Famvir Pregnancy Registry. Physicians are encouraged to register their patients by calling (888) 669-6682.

Nursing Mothers

Following oral administration of famciclovir to lactating rats, penciclovir was excreted in breast milk at concentrations higher than those seen in the plasma. It is not known whether it is excreted in human milk. There are no data on the safety of Famvir in infants.

Usage in Children

Safety and efficacy in children under the age of 18 years have not been established.

Geriatric Use

Of 816 patients with herpes zoster in clinical studies who were treated with Famvir, 248 (30.4%) were ≥65 years of age and 103 (13%) were ≥75 years of age. No overall differences were observed in the incidence or types of adverse events between younger and older patients.

Of 610 patients with recurrent herpes simplex (type 1 or type 2) in clinical studies who were treated with Famvir, 26 (4.3%) were ≥65 years of age and 7 (1.1%) were ≥75 years of age. Clinical studies of Famvir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In general, appropriate caution should be exercised in the administration and monitoring of FAMVIR in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Immunocompetent Patients

The safety of Famvir® (famciclovir) has been evaluated in clinical studies involving 816 Famvir-treated patients with herpes zoster (Famvir, 250 mg t.i.d. to 750 mg t.i.d.); 163 Famvir-treated patients with recurrent genital herpes (Famvir, 1000 mg b.i.d.); 1,197 patients with recurrent genital herpes treated with Famvir as suppressive therapy (125 mg q.d. to 250 mg t.i.d.) of which 570 patients received Famvir (open-labeled and/or double-blind) for at least 10 months; and 447 Famvir-treated patients with herpes labialis (Famvir, 1500 mg once or 750 mg b.i.d.). Table 5 lists selected adverse events.

Table 5
Selected Adverse Events (all grades and without regard to causality) Reported by
≥2% of Patients in Placebo-controlled Famvir® (famciclovir) Trials*

Event	Incidence							
	Herpes Zoster†		Recurrent Genital Herpes†		Genital Herpes-Suppression†		Herpes Labialis†	
	Famvir® 500 mg t.i.d.* (n=273) %	Placebo (n=146) %	Famvir® 1 gram b.i.d.* (n=163) %	Placebo (n=166) %	Famvir® 250 mg b.i.d.* (n=458) %	Placebo (n=63) %	Famvir® 1500 mg single dose* (n=227) %	Placebo (n=254) %
Nervous System								
Headache	22.7	17.8	13.5	5.4	39.3	42.9	9.7	6.7
Paresthesia	2.6	0.0	0.0	0.0	0.9	0.0	0.0	0.0
Migraine	0.7	0.7	0.6	0.6	3.1	0.0	0.0	0.0
Gastrointestinal								
Nausea	12.5	11.6	2.5	3.6	7.2	9.5	2.2	3.9
Diarrhea	7.7	4.8	4.9	1.2	9.0	9.5	1.8	0.8
Vomiting	4.8	3.4	1.2	0.6	3.1	1.6	0.0	0.0
Flatulence	1.5	0.7	0.6	0.0	4.8	1.6	0.0	0.0
Abdominal Pain	1.1	3.4	0.0	1.2	7.9	7.9	0.0	0.4
Body as a Whole								
Fatigue	4.4	3.4	0.6	0.0	4.8	3.2	1.3	0.4
Skin and Appendages								
Pruritus	3.7	2.7	0.0	0.6	2.2	0.0	0.0	0.0
Rash	0.4	0.7	0.0	0.0	3.3	1.6	0.0	0.0
Reproductive Female								
Dysmenorrhea	0.0	0.7	1.8	0.6	7.6	6.3	0.9	0.0

*Patients may have entered into more than one clinical trial.

†7 days of treatment

‡1 day of treatment

§daily treatment

The following adverse events have been reported during post-approval use of Famvir: urticaria, hallucinations and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly). Because these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Table 6 lists selected laboratory abnormalities in genital herpes suppression trials.

Table 6
Selected Laboratory Abnormalities in Genital Herpes Suppression Studies*

Parameter	Famvir® (n=660)† %	Placebo (n=210)† %
Anemia (<0.8 x NRL)	0.1	0.0
Leukopenia (<0.75 x NRL)	1.3	0.9
Neutropenia (<0.8 x NRL)	3.2	1.5
AST (SGOT) (>2 x NRH)	2.3	1.2
ALT (SGPT) (>2 x NRH)	3.2	1.5
Total Bilirubin (>1.5 x NRH)	1.9	1.2
Serum Creatinine (>1.5 x NRH)	0.2	0.3
Amylase (>1.5 x NRH)	1.5	1.9
Lipase (>1.5 x NRH)	4.9	4.7

*Percentage of patients with laboratory abnormalities that were increased or decreased from baseline and were outside of specified ranges.

†n values represent the minimum number of patients assessed for each laboratory parameter.

NRH = Normal Range High.

NRL = Normal Range Low.

HIV-Infected Patients

In HIV-infected patients, the most frequently reported adverse events for famciclovir (500 mg twice daily; n=150) and acyclovir (400 mg, 5x/day; n=143), respectively, were headache (16.7% vs. 15.4%), nausea (10.7% vs. 12.6%), diarrhea (6.7% vs. 10.5%), vomiting (4.7% vs. 3.5%), fatigue (4.0% vs. 2.1%), and abdominal pain (3.3% vs. 5.6%).

Post Marketing Experience

The following adverse events have been reported during post-approval use of Famvir: urticaria, serious skin reactions (e.g., erythema multiforme), jaundice, thrombocytopenia, hallucinations, dizziness, somnolence and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly). Because these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

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