

Cloudy Cervical Discharge Tied to *M. genitalium*

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CHICAGO — A cloudy cervical exudate observed on clinical exam is strongly associated with *Mycoplasma genitalium* infections, especially among women older than 25 years.

The age correlation suggests a different immunologic response to the bacterium among older women, and may partially explain the conflicting literature regarding the

association of *M. genitalium* and cervicitis, Lisa Manhart, Ph.D., said at a conference on STD prevention sponsored by the Centers for Disease Control and Prevention.

Dr. Manhart and her associates examined *M. genitalium* infections among 1,038 women aged 14-46 years who attended a public STD clinic from 2000 to 2006. *M. genitalium* infection was determined by either polymerase chain reaction or transcription-mediated amplification assay.

M. genitalium was detected in 119

women (11%). Of these, five (4%) were coinfecting with gonorrhea and seven (6%) with chlamydia, said Dr. Manhart of the University of Washington, Seattle.

Women with *M. genitalium* were significantly younger than those without (24 vs. 27 years), and significantly more likely to be black (57% vs. 35%). They had a significantly younger age at sexual debut (15 vs. 16 years), were more likely to be current smokers, and were less likely to be taking oral contraceptives. There were no

significant associations with sexual behaviors (other than debut) or with the time since their last sexual encounter.

The incidence of mucopurulent cervicitis was not significantly different between those with and without infection (14% vs. 9%). The incidence of mild cervicitis was also similar between groups. "The majority of women in both groups had very low levels of polymorphonuclear neutrophils (up to 14 per high-magnification field)," Dr. Manhart said.

"However, we did see a significant difference when we looked at the incidence of cloudy cervical discharge. This was present in 22% of the women with *M. genitalium* infections, but only in 12% of those without the infection," she said.

This pattern was consistent in a multivariate analysis that adjusted for other known causes of mucopurulent cervicitis and cloudy discharge, including gonorrhea and chlamydia infections and the use of oral contraceptives, Dr. Manhart said.

After adjusting for these factors, women



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with mucopurulent cervicitis had a modest, but nonsignificant, 60% increased risk of the infection, compared with those without mucopurulent cervicitis. Women with cloudy cervical discharge, however, were twice as likely to have the infection as those without cloudy discharge—a significantly increased risk.

Of eight studies which have examined the association of *M. genitalium* and cervicitis, four have found a significant association, while four have not, Dr. Manhart said. "The studies that showed an association looked at populations with broad age groups, ranging from 18 years to the mid-40s, while those that showed no relationship were conducted in adolescent populations or among very young college students."

The researchers investigated the impact of age on the risk of *M. genitalium* infection and cervicitis. Although the infection was more prevalent among younger women, they were less likely than older women to show an association between *M. genitalium* and cervicitis. In women younger than 25 years, there was no significant relationship between the infection and either mucopurulent cervicitis or cloudy discharge. But women older than 25 years who had *M. genitalium* were 2.5 times more likely to have mucopurulent discharge and 2.4 times more likely to have cloudy cervical discharge than women under 25 years.

"This suggests that older women have a different immunologic response to *M. genitalium* than do younger women," Dr. Manhart said. "While we think these results are interesting and intriguing, we really can't draw any conclusions about causality."

Dr. Manhart reported no financial disclosures related to the study. ■

Postmarketing Experience—Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported very rarely since market introduction include retinal vein occlusion, stroke, and death associated with venous thromboembolism (VTE).

DRUG INTERACTIONS: Cholestyramine—Concomitant administration of cholestyramine with EVISTA is not recommended. Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect. EVISTA should not be co-administered with other anion exchange resins [see *Clinical Pharmacology*].

Warfarin—If EVISTA is given concomitantly with warfarin or other warfarin derivatives, prothrombin time should be monitored more closely when starting or stopping therapy with EVISTA [see *Clinical Pharmacology*].

Other Highly Protein-Bound Drugs—EVISTA should be used with caution with certain other highly protein-bound drugs such as diazepam, diazoxide, and lidocaine. Although not examined, EVISTA might affect the protein binding of other drugs. Raloxifene is more than 95% bound to plasma proteins [see *Clinical Pharmacology*].

Systemic Estrogens—The safety of concomitant use of EVISTA with systemic estrogens has not been established and its use is not recommended.

Other Concomitant Medications—EVISTA can be concomitantly administered with ampicillin, amoxicillin, antacids, corticosteroids, and digoxin [see *Clinical Pharmacology*].

The concomitant use of EVISTA and lipid-lowering agents has not been studied.

USE IN SPECIFIC POPULATIONS: Pregnancy—Pregnancy Category X. EVISTA should not be used in women who are or may become pregnant [see *Contraindications*].

Nursing Mothers—EVISTA should not be used by lactating women [see *Contraindications*]. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when raloxifene is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—Of the total number of patients in placebo-controlled clinical studies of EVISTA, 61% were 65 and over, while 15.5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on clinical trials, there is no need for dose adjustment for geriatric patients [see *Clinical Pharmacology*].

Renal Impairment—EVISTA should be used with caution in patients with moderate or severe renal impairment [see *Warnings and Precautions and Clinical Pharmacology*].

Hepatic Impairment—EVISTA should be used with caution in patients with hepatic impairment [see *Warnings and Precautions and Clinical Pharmacology*].

OVERDOSAGE: In an 8-week study of 63 postmenopausal women, a dose of raloxifene HCl 600 mg/day was safely tolerated. In clinical trials, no raloxifene overdose has been reported.

In postmarketing spontaneous reports, raloxifene overdose has been reported very rarely (less than 1 out of 10,000 [$<0.01\%$] patients treated). The highest overdose has been approximately 1.5 grams. No fatalities associated with raloxifene overdose have been reported. Adverse reactions were reported in approximately half of the adults who took ≥ 180 mg raloxifene and included leg cramps and dizziness.

Two 18-month-old children each ingested raloxifene 180 mg. In these two children, symptoms reported included ataxia, dizziness, vomiting, rash, diarrhea, tremor, and flushing, as well as elevation in alkaline phosphatase.

There is no specific antidote for raloxifene.

No mortality was seen after a single oral dose in rats or mice at 5000 mg/kg (810 times the human dose for rats and 405 times the human dose for mice based on surface area, mg/m²) or in monkeys at 1000 mg/kg (80 times the AUC in humans).

CLINICAL PHARMACOLOGY: Pharmacokinetics—Special Populations—Pediatric—The pharmacokinetics of raloxifene has not been evaluated in a pediatric population [see *Use in Specific Populations*]. **Geriatric**—No differences in raloxifene pharmacokinetics were detected with regard to age (range 42 to 84 years) [see *Use in Specific Populations*]. **Gender**—Total extent of exposure and oral clearance, normalized for lean body weight, are not significantly different between age-matched female and male volunteers. **Race**—Pharmacokinetic differences due to race have been studied in 1712 women, including 97.5% White, 1.0% Asian, 0.7% Hispanic, and 0.5% Black in the osteoporosis treatment trial and in 1053 women, including 93.5% White, 4.3% Hispanic, 1.2% Asian, and 0.5% Black in the osteoporosis prevention trials. There were no discernible differences in raloxifene plasma concentrations among these groups; however, the influence of race cannot be conclusively determined. **Renal Impairment**—In the osteoporosis treatment and prevention trials, raloxifene concentrations in women with mild renal impairment are similar to women with normal creatinine clearance. When a single dose of 120 mg raloxifene HCl was administered to 10 renally impaired males [7 moderate impairment (CrCl = 31–50 mL/min); 3 severe impairment (CrCl ≤ 30 mL/min)] and to 10 healthy males (CrCl >80 mL/min), plasma raloxifene concentrations were 122% (AUC_{0-∞}) higher in renally impaired

patients than those of healthy volunteers. Raloxifene should be used with caution in patients with moderate or severe renal impairment [see *Warnings and Precautions and Use in Specific Populations*]. **Hepatic Impairment**—The disposition of raloxifene was compared in 9 patients with mild (Child-Pugh Class A) hepatic impairment (total bilirubin ranging from 0.6 to 2 mg/dL) to 8 subjects with normal hepatic function following a single dose of 60 mg raloxifene HCl. Apparent clearance of raloxifene was reduced 56% and the half-life of raloxifene was not altered in patients with mild hepatic impairment. Plasma raloxifene concentrations were approximately 150% higher than those in healthy volunteers and correlated with total bilirubin concentrations. The pharmacokinetics of raloxifene has not been studied in patients with moderate or severe hepatic impairment. Raloxifene should be used with caution in patients with hepatic impairment [see *Warnings and Precautions and Use in Specific Populations*].

Drug Interactions—Cholestyramine—Cholestyramine, an anion exchange resin, causes a 60% reduction in the absorption and enterohepatic cycling of raloxifene after a single dose. Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect [see *Drug Interactions*].

Warfarin—In vitro, raloxifene did not interact with the binding of warfarin. The concomitant administration of EVISTA and warfarin, a coumarin derivative, has been assessed in a single-dose study. In this study, raloxifene had no effect on the pharmacokinetics of warfarin. However, a 10% decrease in prothrombin time was observed in the single-dose study. In the osteoporosis treatment trial, there were no clinically relevant effects of warfarin co-administration on plasma concentrations of raloxifene [see *Drug Interactions*]. **Other Highly Protein-Bound Drugs**—In the osteoporosis treatment trial, there were no clinically relevant effects of co-administration of other highly protein-bound drugs (e.g., gemfibrozil) on plasma concentrations of raloxifene. In vitro, raloxifene did not interact with the binding of phenytoin, tamoxifen, or warfarin (see above) [see *Drug Interactions*].

Ampicillin and Amoxicillin—Peak concentrations of raloxifene and the overall extent of absorption are reduced 28% and 14%, respectively, with co-administration of ampicillin. These reductions are consistent with decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, the systemic exposure and the elimination rate of raloxifene were not affected. In the osteoporosis treatment trial, co-administration of amoxicillin had no discernible differences in plasma raloxifene concentrations [see *Drug Interactions*]. **Antacids**—Concomitant administration of calcium carbonate or aluminum and magnesium hydroxide-containing antacids does not affect the systemic exposure of raloxifene [see *Drug Interactions*]. **Corticosteroids**—The chronic administration of raloxifene in postmenopausal women has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose [see *Drug Interactions*]. **Digoxin**—Raloxifene has no effect on the pharmacokinetics of digoxin [see *Drug Interactions*]. **Cyclosporine**—Concomitant administration of EVISTA with cyclosporine has not been studied. **Lipid-lowering agents**—Concomitant administration of EVISTA with lipid-lowering agents has not been studied.

PATIENT COUNSELING INFORMATION: See FDA-approved Medication Guide.

Physicians should instruct their patients to read the Medication Guide before starting therapy with EVISTA and to reread it each time the prescription is renewed.

Osteoporosis Recommendations, Including Calcium and Vitamin D Supplementation—For osteoporosis treatment or prevention, patients should be instructed to take supplemental calcium and/or vitamin D if intake is inadequate. Patients at increased risk for vitamin D insufficiency (e.g., over the age of 70 years, nursing home bound, chronically ill, or with gastrointestinal malabsorption syndromes) should be instructed to take additional vitamin D if needed. Weight-bearing exercises should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Patient Immobilization—EVISTA should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and patients should be advised to avoid prolonged restrictions of movement during travel because of the increased risk of venous thromboembolic events [see *Warnings and Precautions*].

Hot Flashes or Flushes—EVISTA may increase the incidence of hot flashes and is not effective in reducing hot flashes or flushes associated with estrogen deficiency. In some asymptomatic patients, hot flashes may occur upon beginning EVISTA therapy.

Reduction in Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis or at High Risk of Invasive Breast Cancer—Use of EVISTA is associated with the reduction of the risk of invasive breast cancer in postmenopausal women. EVISTA has not been shown to reduce the risk of noninvasive breast cancer. When considering treatment, physicians need to discuss the potential benefits and risks of EVISTA treatment with the patient.

EVISTA is not indicated for the treatment of invasive breast cancer or reduction of the risk of recurrence.

Patients should have breast exams and mammograms before starting EVISTA and should continue regular breast exams and mammograms in keeping with good medical practice after beginning treatment with EVISTA.

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