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INSIDE

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Trichomonas Infection — It's Not Just a Girl Thing, But the Guys Don't Know It

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Source: Seña AC, et al. *Trichomonas vaginalis* infection in male sexual partners: implications for diagnosis, treatment, and prevention. *Clin Infect Dis.* 2007;44:13-22.

Synopsis: *Using multiple testing modalities, including a sensitive PCR, it was found that almost three-fourths of male sexual partners of women with vaginal trichomoniasis were also infected with this protozoan.*

Male sexual partners of women with vaginal trichomoniasis were tested, using urethral and urine culture, as well as urine polymerase chain reaction (PCR), for evidence of infection with this flagellated protozoan. Approximately one-fourth of the women were asymptomatic, but one-half also had Gram stain evidence of bacterial vaginosis; 1.4% of those tested were HIV positive.

At least one of the 3 tests was positive in 177 of 256 (71.7%) of the male sex partners from whom samples were obtained, with PCR being the most sensitive. Only 41 (23.2%) of those with a positive test were symptomatic. Approximately 10% were co-infected with either *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. None of the 69 tested were HIV infected. In multivariate analysis, a vaginal pH > 4.5 and younger male age were each independently associated with an increased risk of concordant trichomoniasis.

COMMENTARY

Trichomoniasis is the most common non-viral sexually transmitted infection throughout the world. Evidence indicates that infection with *Trichomonas vaginalis* is not a trivial issue. Vaginal trichomoniasis appears to be associated with an increased risk of acquisition of HIV infection, as well as with complications such as pelvic inflammatory disease, and with adverse pregnancy outcomes. While most symptomatic cases occur in women, infection has been known to be common in their male (as well as female) sexual partners. Infection in men is, however,

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more frequently than not asymptomatic. As a whole, the available information suggests that consideration should be given to the development of public health programs designed to screen asymptomatic individuals, both male and female, for evidence of trichomonal infection.

Symptomatic women complain of vaginal discharge and vulvar irritation and most characteristically have a diffuse, yellow-green malodorous discharge. Men who are symptomatic have urethritis. The classical means of diagnosis in women is microscopic examination of vaginal secretions, but, relative to culture, this procedure has a sensitivity of only 60% to 70% — and is even less effective in the diagnosis of trichomonal urethritis in men. At least 2 rapid point-of-care tests, each of which has a reported sensitivity > 83% and specificity >97% relative to culture, have received FDA approval in the United States. One, an immunochromatographic capillary flow dipstick test (OSOM Trichomonas Rapid Test, Genzyme Diagnostics, Cambridge, Massachusetts) can provide results in 10 minutes, while the Affirm™ VP III, a nucleic acid probe test, requires 45 minutes.[1] No commercial nucleic acid amplification test is available in the United States. Culture on media, such as Diamond's TYM, is usually positive within 48 hours, but requires 7 -10 days of incubation before the culture can be deemed to be negative.

The CDC recommends treatment with either metronidazole or tinidazole — there are no proven effective alternatives to the use of nitroimidazoles.[1] The preferred regimens are a single 2-gram dose of either drug, while an alternative regimen is 500 mg metronidazole twice daily for 7 days. Topical formulations of metronidazole achieve cure rates of only approximately 50%. Sexual partners should also be treated. Follow-up is not necessary in patients whose symptoms resolve. However, low-level resistance to metronidazole occurs in 2% to 5% of cases, and high-level resistance has also been reported. If symptomatic infection persists after treatment with metronidazole and the sexual partners have also been treated, the 5-day bid course of metronidazole or a single dose of tinidazole can be used. If both of these fail, the CDC recommends giving either drug in a dose of 2 grams daily for 5 days. The CDC offers in vitro susceptibility testing for selected isolates. ■

Reference

1. CDC. Sexually transmitted diseases treatment guidelines, 2006. *MMWR*. 2006; 55(RR11); 1-94. http://www.cdc.gov/ mmwr/preview/mmwrhtml/ rr5511a1.htm. Accessed Jan. 7, 2007.

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First Chemokine Receptor Antagonist Available Under Expanded Access

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor of Medicine, Stanford University School of Medicine

Dr. Winslow is a consultant for Bayer Diagnostics, and on the speaker's bureau for GlaxoSmithKline and Pfizer.

UK-427,857 (MARAVIROC) IS AN INVESTIGATIONAL small-molecule HIV entry inhibitor that binds to the CCR5 chemokine receptor on the surface of T-cells. This chemokine receptor is normally the receptor for the chemokines MIP-1 alpha and RANTES.[1] In HIV infection after initial binding of HIV's external envelope protein, gp120, to CD4, conformational change occurs in the trimeric structure of gp120 allowing its binding to generally one of 2 co-receptors (CCR5 or CXCR4, the latter being the normal receptor for SDF-1). Following this, regions of the transmembrane glycoprotein, gp41, fuse with the cell membrane, followed by uncoating of the virus with vRNA being reverse transcribed within the cytoplasm of the host cell. In acute and early HIV infection, virus isolated from most patients generally displays tropism for the CCR5 co-receptor (R5 virus). Later as infection progresses, one commonly observes switch of virus co-receptor usage to CXCR4 (X4) or dual tropism with the virus able to use both co-receptors. In vitro, R5

virus tends to be monocytotropic, but can be cultured in PHA/IL-2 stimulated PBMC's, whereas X4 virus tends to not be monocytotropic but can be cultured in lymphoblastoid cell lines such as MT-2 as well as stimulated PBMC's. HIV co-receptor tropism can be examined in vitro traditionally by a virus's ability to grow in T-cell lines (CXCR4 tropism) and can also be determined by various recombinant viral assays.

The only currently commercially available attachment/entry inhibitor is enfuvirtide (Fuzeon), which blocks the gp41-mediated membrane fusion event. Unfortunately enfuvirtide is a large recombinant molecule that is not orally bioavailable, requires twice daily subcutaneous injection, and is often poorly tolerated due to painful injection-site reactions. Maraviroc is a small molecule with good oral bioavailability that binds noncompetitively to CCR5, causing a conformational change in the extracellular loops of CCR5 that renders it unrecognizable to wild type R5-tropic HIV. While retaining activity against HIV resistant to the traditional 3 classes of antiretrovirals, maraviroc has no activity against viruses that use CXCR4 for cell entry.[2] Maraviroc is a substrate for the cytochrome P450 3A/4 isoform and P-glycoprotein. Therefore, plasma levels are increased by Cyp 3A4 inhibitors such as ritonavir and antifungal azoles and levels are decreased by enzyme inducers such as rifampin and efavirenz.

In short term monotherapy trials in treatment naïve patients a clear dose-response antiretroviral effect was observed with plateau of antiretroviral effect at maraviroc doses ≥ 100 mg BID. Mean viral load reductions were about 1.5 $\log_{10}$. Most studies conducted in treatment experienced patients are still ongoing. The drug is well-tolerated with no substantial difference in frequency of adverse events between the maraviroc and placebo arms.

COMMENTARY

Maraviroc represents a potentially exciting new approach to treat HIV infection based on its mechanism of action inhibiting virus co-receptor binding. While controlled clinical trials are still ongoing, a number of issues may limit the eventual clinical utility of this drug (and other co-receptor inhibitors in development with other pharmaceutical companies). These include: (1) Relative weak potency compared to existing agents such as nnRTIs and PIs (and other investigational agents such as the integrase inhibitors) where 2-3 $\log_{10}$ reductions of HIV RNA are observed in treatment naïve individuals. (2) The fact that R5 tropic HIV is relatively rare in patients who have advanced infection and have failed first and second line antiretroviral regimens. (3) Possible selection of X4 tropic virus in vivo with the potential for accelerated disease progression. (Fortunately, this possibility does not appear to be likely based on at least one Pfizer-sponsored trial conducted in patients infected with X4 or dual R5/X4 tropic virus where maraviroc appeared to confer neither harm nor benefit.)

The Pfizer HIV EAP Program is being coordinated by the Contract Research Organization, Parexel (1-888-275-4478). The study is open label and is open to treatment-experienced patients with R5-tropic HIV who have limited therapeutic options. Patients must have an HIV RNA > 1,000 copies/mL. Maraviroc will be added to an investigator selected Optimized Background Therapy (OBT) regimen. Because of pharmacokinetic interactions as noted above, patients will be dosed at 300 mg BID (or daily) if dosed with tipranavir/ritonavir or nucleosides in the absence of potent CYP3A4 inhibitors or inducers; 150 mg BID (or daily) when dosed with other ritonavir boosted PIs, clarithromycin or antifungal imidazoles; and 600 mg BID (or daily) when dosed with a potent CYP3A4 inducer such as efavirenz or rifampin. ■

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Posaconazole Salvage in Invasive Aspergillosis

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Source: Walsh TJ, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis.* 2007;44:2-12.

Synopsis: *Salvage therapy of invasive aspergillosis with posaconazole was associated with a 42% response rate, compared to only 26% in an external control group.*

In a multicenter international open-label study, patients with proven or probable invasive aspergillosis (IA) that was refractory to standard antifungal therapy or who were intolerant to such therapy were treated with posaconazole in a total daily amount of 800 mg administered in divided doses. In addition to the 107 posaconazole recipients meeting criteria for analysis, 86 control subjects with proven or probable IA

who received other salvage therapies were included in the assessment. Among the latter group, salvage treatments were approximately evenly distributed among amphotericin B, itraconazole, a combination of the 2, and other agents. The median duration of posaconazole therapy was 56 days, while controls received their salvage therapy for only 22 days. Patients of either group receiving mechanical ventilation at baseline or who died within 72 hours were excluded from the analysis.

Three-fourths of patients had a hematological malignancy and approximately one-half of the total population had received a hematopoietic stem cell transplant, most of which were allogeneic. Twelve percent of posaconazole recipients and 21% of controls had been intolerant of standard antifungal therapy, while the remainder had suffered from infections refractory to treatment. Infection was confined to the lungs in approximately three-fourths of cases.

Success of antifungal therapy was achieved in 42% of posaconazole recipients and 26% of control subjects (OR, 4.06; 95% CI, 1.50 to 11.04; P =0.06). Success was associated with higher posaconazole serum concentrations, ranging from 24% in those whose concentrations fell into the lowest quartile (mean Cmax of 142 ng/ml) to 75% in those in the highest quartile (mean Cmax of 1489 ng/ml). Only 4 of 14 (29%) of patients with *Aspergillus terreus* infection responded to salvage with posaconazole as did only 2 of 13 (15%) receiving alternative salvage therapies, however.

Posaconazole therapy was also associated with greater survival than were the other salvage therapies received by control group members. Posaconazole was well tolerated with gastrointestinal disturbances being the most frequently reported adverse events.

COMMENTARY

The 42% rate of success in patients with IA receiving salvage treatment with posaconazole may seem low but is, in fact, remarkably similar to the results of salvage therapy with other antifungals, which have ranged from 38% with voriconazole to 45% with caspofungin. Furthermore, the response rate to posaconazole therapy in this study was superior to that of an external prospectively selected control group. Thus, posaconazole appears to be an effective salvage agent in patients with IA. However, voriconazole, on the basis of the results of a randomized clinical trial demonstrating its superiority to amphotericin B deoxycholate,[1] remains the initial treatment of choice for most patients with IA. In addition, clinical practice at many centers has evolved toward the use of combination therapy with the addition of an echinocandin, most commonly caspofungin, to voriconazole in that setting. Of note is that none of the patients in this study received either voriconazole or an echinocandin as part of their initial failed regimen.

The low response rate in patients infected with *A. terreus* is consistent with results seen with other antifungals. This organism appears to be emerging as a problem pathogen because of its relative refractoriness to antifungal therapy. This poor response to therapy is true despite the fact that the MIC90 of many antifungals against this species is similar to that of species that exhibit higher rates of response to therapy.[2] Thus, the posaconazole MIC90 of *A. terreus* is reported to be 1000 ng/ml while that of *A. fumigatus* is only one dilution lower at 500 ng/ml.[2] As indicated above, a higher posaconazole Cmax (mean of 1489 ng/ml in the highest quartile) was associated with better outcomes.

Posaconazole is only available as an oral suspension and its bioavailability is maximized by split dosing and by administration with food. The finding of an association of improved responses with higher serum concentrations of this drug demonstrate a need to pay attention to these factors in order to optimize bioavailability. In addition, the apparent dose response seen in this study suggests the possibility that pushing the dose beyond that currently recommended may prove beneficial, but the efficacy and safety of such an approach requires further study. ■

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Catheter-Related Bloodstream Infections: Doing the Right Thing Pays Off

ABSTRACT & COMMENTARY

By Robert Muder, MD

Hospital Epidemiologist, Pittsburgh VA Medical Center

Dr. Muder does research for Aventis and Pharmacia.

Synopsis: *In a study involving 108 ICUs in Michigan, an evidence-based intervention led to a 66% reduction in catheter-related bloodstream infections that was sustained over an 18-month period.*

Source: Pronovost P, et al. An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU. *N Engl J Med.* 2006;355:2725-2732.

PRONOVOST AND COLLEAGUES CONDUCTED A MULTI-hospital cohort study aimed at reducing the rate of catheter-related bloodstream infections (CRBSIs) in

ICUs. The intervention focused on increasing adherence to evidence-based CDC recommendations for catheter insertion. In summary, these are:

1. Hand hygiene,
2. Full-barrier precautions during insertion,
3. Skin cleansing with chlorhexidine,
4. Avoiding the femoral insertion site,
5. Removal of unnecessary catheters.

Each ICU designated a physician and nurse to serve as team leaders, who were given instruction in patient safety, the CDC guidelines, and data collection. In collaboration with the local infection control practitioners, the teams provided education to clinicians regarding the CDC guidelines. Incentives to compliance included providing a central-line insertion cart with all necessary supplies, discussion of catheter removal at daily rounds, a checklist to document compliance during catheter insertion, and regular feedback regarding the number and rate of CRBSIs in the unit. Unit staff were encouraged to stop providers from inserting catheters if insertion technique did not follow recommendations.

One hundred eight hospitals joined the study, and 103 participated. This represented 85% of all ICU beds in Michigan. The final analysis included 375,757 catheter days. During the baseline (pre-intervention) period the median rate of CRBSIs was 2.7/1000 patient days (range 0.6 - 4.8). Following intervention the median rate was 0 (range 0 - 3.0); this was sustained for 18 months of follow up. In fact, the rate of CRBSI fell progressively during follow up. The incidence rate ratio was 0.62 during the first quarter after intervention, falling to 0.34 by the final quarter. To put it another way, at the end of the study, the rate of CRBSIs was 66% less than at baseline.

COMMENTARY

According to CDC estimates, approximately 50,000 CRBSIs occur in the United States annually. Attributable mortality is as high as 35%, and excess cost per episode is in greater than $40,000. The CDC has recently issued evidence based recommendations for catheter insertion. If these guidelines are indeed effective, and if they are widely implemented, the potential number of lives and dollars that would be saved is enormous.

I have little doubt that the infection control manuals of the vast majority of U.S. hospitals mandate adherence to the CDC guidelines for central catheter insertion. Whether or not providers actually do so is, of course, another matter entirely. There is ample evidence that purely educational endeavors don't change practice appreciably. Infection control practitioners have neither the time nor the authority to provide monitoring or enforcement. The study by Pronovost and colleagues demonstrates that a different approach can work admirably. Several key aspects of the strategy deserve emphasis. First, team leaders, consisting of a doctor and nurse, were recruited from ICUs in each hospital. These leaders would likely be highly visible on the units, and well known to the physicians and staff. The team leaders received training in the appropriate precautions, and were thus in a position to disseminate this knowledge to their colleagues. Second, compliance was made easier by providing all the necessary materials on a central-line insertion cart. Third, the unit staff received regular and timely feedback on infection rates from the team leaders. Finally, unit staff were given "permission" to prevent catheter insertion when appropriate precautions were not being taken.

The study has some shortcomings. First, it is a quasi-experimental, or "before and after" study, and thus there is no control group of ICUs. The authors note that finding a control group was difficult because all of the participating hospitals wanted to implement the intervention. However, there is no evidence that there was any other intervention or spontaneous trend that could account for the marked decrease in CRBSIs. The sheer number of hospitals and of catheter days, coupled with the fact that different hospitals started the intervention at different times, makes the results credible. One could have wished that the hospitals had reported rates of compliance with the CDC guidelines and correlated that with reduction in bacteremia rates. That is a rather minor flaw given the magnitude of the result.

I believe that 2 major points deserve emphasis. The first is that CRBSIs are clearly preventable. A major reduction in incidence can occur with a rather modest investment of time and money. There seems little reason why all ICUs should not embark on a similar intervention. The second is that the intervention used in this study is a model that ought to be readily adaptable to a wide variety of patient safety issues. In many cases, we know what ought to be done; actually getting it done is has always been the problem. ■

New Oral Treatment for Chronic Hepatitis B: Telbivudine

SPECIAL REPORT

By Nam Do and Jessica C. Song

Nam Do is a pharmacy resident, Santa Clara Valley Medical Center, and Jessica C. Song, MA, PharmD, is Pharmacy Residency Coordinator, Santa Clara Valley Medical Center.

Nam Do and Jessica C. Song report no financial relationships relevant to this field of study.

TREATMENT OF CHRONIC HEPATITIS B IS DIRECTED AT SUPpressing viral replication, reducing hepatitis (necroinflammatory) activity, slowing progression of fibrotic disease, inducing loss of HBeAg with seroconversion to anti-HBe, and rendering patients noninfectious.[1] At present, 4 oral antiviral agents, entecavir, adefovir dipivoxil, lamivudine,

and telbivudine are FDA (Food and Drug Administration)-approved for the treatment of chronic hepatitis B, with telbivudine receiving FDA approval in October 2006.[2] This article will: (1) review the pharmacology, pharmacokinetics, and FDA indications of telbivudine, (2) review the safety and efficacy of telbivudine, and (3) review the drug interactions and dosage of this new nucleoside analog.

Pharmacologic Properties

Telbivudine is a thymidine nucleoside analog with activity against hepatitis B virus (HBV) DNA polymerase that undergoes phosphorylation to the active triphosphate form.[3] Telbivudine 5'-triphosphate competes with the natural substrate thymidine 5'-triphosphate and therefore inhibits HBV DNA Polymerase. Inhibition of HBV viral replication occurs following incorporation of telbivudine 5'-triphosphate into viral DNA.

Telbivudine undergoes minimal metabolism, as the majority of the drug is eliminated unchanged in urine by passive diffusion, with the renal clearance of this drug approaching HBeAg (+) (-) glomerular filtration rate.[3] Telbivudine is indicated for the treatment HBeAg (+) and HBeAg(-) patients with treatment-naïve chronic HBV, who have evidence of histologically active disease or persistent elevations in serum aminotransferases, and with evidence of viral replication.[3]

Telbivudine is generally well-tolerated, with the following adverse events occurring in ≥ 9% of patients taking this drug: upper respiratory tract infection (14%), fatigue/malaise (12%), abdominal pain (12%), nasopharyngitis (11%), headache (11%), and elevated blood creatine phosphokinase (CPK; 9%).[3] Since severe lactic acidosis (± hepatomegaly with steatosis) and severe acute exacerbations of HBV following product discontinuation have been reported with the use of multiple nucleoside analogs,[4-6] the FDA mandated the manufacturer of telbivudine to place black-box warnings in the monograph of this agent.[3]

The potential for CYP450 (Cytochrome P450) - mediated interactions is low for telbivudine, as it does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2B6, CYP2E1, or CYP3A4. Moreover, telbivudine is not a substrate of any of the commonly seen CYP isoenzymes (*refer to above*). However, the manufacturer advises precautions with concurrent use of this agent with known nephrotoxic drugs.[3] Table 1 summarizes the key pharmacologic properties of telbivudine.

Resistance Patterns,Clinical Efficacy for Treatment of HBV

At present, 4 oral drugs (telbivudine, entecavir, adefovir dipivoxil, lamivudine) and one pegylated interferon product (peginterferon alfa-2a) have been approved by the FDA for use in the management of chronic HBV infection.[1] Emergence of resistance (via YMDD mutation) has been associated with lamivudine therapy, developing in 14% of patients after one year of therapy and in up to 69% of patients after 5 years of therapy.[1] Viral resistance appears to be less likely to develop during adefovir dipivoxil therapy, as mutant rtN236T (or rtA181V/T) has been identified in up to 29% of patients after 5 years of therapy. To date, the emergence of entecavir resistance among treatment-naïve HBV patients has been shown to be a rare occurrence, as one study showed that none of the patients exhibited resistance during 2 years of treatment.[7] However, the incidence of entecavir resistance among lamivudine-refractory patients is estimated to be nearly 10% after 2 years of therapy.[7] The incidence of resistance associated with telbivudine therapy has not been established, but a Phase III clinical trial (GLOBE) showed that 2% of HBeAg(-) patients and 3% of HBeAg(+) patients became resistant to this drug after 52 weeks of therapy.[8]

Recently, an updated HBV treatment algorithm was developed by a panel of U.S. hepatologists and was published in 2006.[1] The panel of hepatologists recommended the use of adefovir, entecavir, or peginterferon alfa-2a as initial therapy of HBeAg (+) and HBeAg(-) patients with elevated HBV DNA and elevated serum aminotransferase levels. The addition of adefovir to lamivudine therapy was recommended for lamivudine-resistant HBV patients, whereas the addition of lamivudine or a switch to entecavir were considered the best treatment options for adefovir-resistant HBV patients. Table 2 summarizes the expert panel's treatment recommendations and Table 3 provides key highlights from clinical trials of peginterferon alfa-2a, lamivudine, entecavir, and adefovir dipivoxil in HBeAg (+) chronic HBV patients.1

Clinical trials of telbivudine have primarily included chronic HBV patients with compensated liver disease and HBeAg (+) patients (2 of 3 studies). Reductions in HBV DNA levels after 24 to 76 weeks of telbivudine therapy have ranged from 6.06 $\log_{10}$ copies/mL to 6.60 $\log_{10}$ copies/mL for HBeAg (+) patients. Of note, telbivudine was shown to be superior to lamivudine[8] and to adefovir[9] in lowering HBV DNA levels in HBeAg (+) patients. In contrast, no difference in the abilities of telbivudine and lamivudine to decrease HBV DNA levels in HBeAg (-) patients were reported in a Phase III study.[8] One Phase III clinical trial showed the superior efficacy of telbivudine compared with that of lamivudine in regards to improvement of the proportion of HBeAg (+) patients achieving ALT normalization and the percentage of patients exhibiting HBeAg loss. However, in HBeAg (-) patients, no difference in efficacy for ALT normalization was observed between telbivudine and lamivudine at 76 weeks.

Interestingly, Phase III clinical trials have shown the superior efficacy of entecavir compared with that of lamivudine in HBeAg (-) and in HBeAg (+) patients when evaluating DNA reduction and ALT normalization.

The rates of HBeAg loss and ALT normalization have been shown to be similar for telbivudine- and adefovir-

Table 1. Pharmacologic Properties of Telbivudine

Brand/Generic[3]	Tyzeka® (Telbivudine)
Classification[3]	Nucleoside analog for treatment of Hepatitis B
Mechanism of Action[3]	L-enantiomer of thymidine, competitively inhibits Hepatitis B Virus (HBV) DNA polymerase. Incorporation of telbivudine 5'-triphosphate into viral DNA causes DNA chain termination.
Indications[3] (FDA labeled)	Tyzeka® (Telbivudine) is indicated for the treatment of the following infections: Chronic hepatitis B in adult patients (HBeAg (+) and HBeAg (-)) with evidence of viral replication and either evidence of persistent elevations in serum ALT/AST or histologically active disease.
Pharmacology (young, healthy adults)[3] **Dose** 600 mg PO daily	Half-life, normal renal/hepatic function (h) 15 C_{max}(mcg/mL) 3.69 +/- 1.25 Tmax (h) 2 Protein bound (%) 3.3% Recovered unchanged in urine (%) 42%
How Supplied[3]	**Oral:** White to slightly yellowish ovaloid-shaped film-coated 600mg tablets, imprinted with "LDT" on one side
Dose[3]	- Chronic Hepatitis B - 600 mg orally daily, with or without food Optimal treatment duration has not been established, but clinical trials have yielded efficacy data from 24-76 weeks - Adult and adolescent patients (note: subjects in pivotal clinical trials were 16 years and older)
Dosage Adjustment[3]	Renal Impairment: - Increase dosing interval to 48 hours (refer to dose above) if CrCl is 30 - 49 ml/min - Increase dosing interval to 72 hours (refer to dose above) if CrCl is <30 ml/min - Increase dosing interval to 96 hours (refer to dose above) if patient has ESRD (including HD or CAPD) - Should be given after hemodialysis on hemodialysis days - Hemodialysis reduces systemic exposure by approximately 23% **Hepatic Impairment:** - No dosage adjustment is required for hepatic insufficiency
Storage/Administration[3]	**Storage:** - Store Tyzeka® tablets in original container at 250C (770F) - Excursions permitted to 15-300C (59-860F) - Keep out of reach of children **Administration:** - 600 mg tablets may be taken with or without food.
Contraindications[3]	- Blood Creatine Kinase (CK), Liver Function Tests (LFTs) and Serum Creatinine (SCr) - Signs and symptoms of lactic acidosis
	Hypersensitivity to any other component of the formulation
Warnings/Precautions[3]	-**Exacerbations of hepatitis after discontinuation of treatment**, monitor LFTs for several months -**Myopathy** reported after weeks to months after initiation of therapy, monitor CK levels and report signs of weakness or muscle pain; therapy should be interrupted if myopathy is suspected and discontinue if myopathy is diagnosed -**Renal Function** Clcr <50 m/min requires dosage adjustment; administration with other drugs that affect renal function may alter plasma levels of Tyzeka® -**Resistance to antiviral drugs for hepatitis B**, no adequate clinical trials have established for efficacy of telbivudine in lamivudine- or adefovir-resistant viral strains -**Liver transplant recipients**, safety and efficacy are unknown in this subset of patients, renal function should be monitored if patient is on cyclosporine, tacrolimus or other drugs affecting renal function
Adverse Effects[3]	**Adverse events occurring in ≥ 9% of patients:** upper respiratory tract infection (14%), fatigue and malaise (12%), abdominal pain (12%), nasopharyngitis (11%), headache (11%), blood CPK increased (9%) Serious adverse effects: lactic acidosis, severe hepatomegaly with steatosis
Drug/Food Interactions[3]	**Drug interactions** with other drugs eliminated by renal excretion are low due to Tyzeka®'s elimination by passive diffusion; other drugs affecting renal function may alter plasma concentrations of Tyzeka®
Pregnancy Category[3]	**B**, to monitor fetal outcomes of pregnant women exposed to telbivudine call 1-800-258-4263
Lactation[3]	Excretion in human milk unknown, mothers should not be advised to breast-feed if taking Tyzeka®
Overdose/Toxicity[3]	**S/Sx:** Subjects who received up to 1800 mg/day for 4 days had no adverse event; lethal dose unknown **Tx:** Includes general supportive care with consideration of hemodialysis
Sounds Like …	Tyzeka® may be confused with: Zyrtec, Celexa, Kayexalate, Tiazac

Table 2. American Gastroenterological Association Institute Recommendations for the Treatment of Chronic Hepatitis B Virus Infection[1]

Type of Infection	Regimen	Duration
HBeAg-Positive or Negative HBV DNA< 20,000 (HBeAg (+)); HBV DNA < 2000 (HBeAg (-)) ALT-Normal (upper limit of normal is 30 IU/L for men, 19 IU/L for females)	No treatment Monitor every 6-12 months (on initial diagnosis, every 3 months for 1y). Consider therapy in patients with known significant histologic disease even if low-level replication.	Not applicable.
HBeAg-Positive or Negative HBV DNA ≥ 20,000 (HBeAg (+)); HBV DNA 2000 (HBeAg (-)) ALT-Normal or Elevated	Low rate of HBeAg seroconversion for all treatments Consider liver biopsy (esp. > 35-40y). If no biopsy, monitor for increased ALT levels Treat if liver is diseased: Adefovir 10 mg PO daily or Entecavir 0.5 mg PO daily or Peginterferon alfa-2a 180 mcg SQ once weekly **Note: if high HBV DNA, adefovir and entecavir are the preferred agents.**	**HBeAg** (+): 6-12 months after HBV DNA levels undetectable. **HBeAg** (-): Entecavir + adefovir are given long-term.
Lamivudine Resistance	Add adefovir 10 mg PO daily (may be preferred over switch to adefovir) Switch to Entecavir 1 mg PO daily (risk for subsequent entecavir resistance) Potential future management: add tenofovir or switch to emtricitabine/tenofovir	Long-term, monitor Q6 months
Adefovir Resistance	Add lamivudine 100 mg PO daily (may be preferred over switch to lamivudine) Switch to entecavir 0.5 mg PO daily (if no prior lamivudine resistance) Potential future therapy: switch to emtricitabine/tenofovir	Long-term, monitor Q6 months
Adefovir Resistance Entecavir Resistance	Add or switch to adefovir or tenofovir	Long-term, monitor Q6 months

Table 3. Comparison of Peginterferon alfa-2a, Lamivudine, Entecavir, and Adefovir Dipivoxil in HBeAg-Positive Chronic HBV[1]

Parameter[a]	Peginterferon alfa-2[a] (lamivudine)[b] 48 wk	Lamivudine (Placebo)[b] 52 wk	Adefovir dipivoxil (Placebo)[b] 48 wk	Entecavir (Lamivudine)[b] 48 wk
Serum HBV DNA loss[c]	25% (40%)	44% (16%)	21% (0%)	67% (36%)
Serum HBV DNA $\log_{10}$	4.5 $\log_{10}$(5.8)	Not available	3.52 $\log_{10}$ (0.55)	6.9 $\log_{10}$(5.4)
HBeAg seroconversion	27% (20%) wk 48 32% (19%) wk 72	16-18% (4-6%) 50% at 5 y	12% (6%) 33%, 96 wk; 46%, 144 wk	21% (18%)
HBeAg loss	30% (22%) wk 48 34% (21%) wk 72	32% (11%)	24% (11%) 46%, 96 wk; 53%, 144 wk	22% (20%)
HBsAg loss	11-25% at 5y in Whites	3% (0%) wk 72 (HBsAg seroconversion)	Insufficient data	2% (1%)
ALT normalization	39% (62%)	41-72% (7-24%)	48% (16%)	68% (60%)
Histologic improvement	38% (34%) wk 72	49-56% (23-25%)	53% (25%)	72% (62%)
Development of resistance	No	14%, to 69% at 5y	0%, 1y; 2%, 2y; 15%, 4y	0% at 1 y and 2y
Durability of response after HBeAg seroconversion	Not available	77% at 37 mo	91% at 55 wk	82% at 24 wk
Dosing regimen	180 mcg weekly x 48 wk (Injection)	100 mg po qday (Oral)	10 mg po qday (Oral)	0.5 mg po qday (Oral)
Tolerability	Poorly tolerated	Well tolerated	Well tolerated	Similar to lamivudine

[a]All data are 1 year unless otherwise stated
[b]Control arm
[c]Lamivudine: hybridization assay with lower limit of detection = 10^5 copies/mL; adefovir: PCR assay (Roche Amplicor Monitor) with lower limit of detection = 400 copies/mL; peginterferon alfa-2a: PCR assay (Roche Cobas) undetectable is < 400 copies/mL; entecavir: PCR assay (Roche Cobas) undetectable is < 300 copies/ml

Table 4. Clinical Trials of Telbivudine for the Treatment of Chronic Hepatitis B

Investigator	Study Design	Primary Endpoint/Patients	Primary Findings
Lai CL, et al (2005)[10]	Multicenter, randomized (1:1:1:1:1), double-blinded Phase 2[b] study (N = 104 total) **Treatment Groups** 1) Telbivudine 400 mg/day; 2) Telbivudine 600 mg/day; 3) Telbivudine 400 mg/day + Lamivudine 100 mg/day (Combo 400); 4) Telbivudine 600 mg/day + Lamivudine 100 mg/day (Combo 600); 5) Lamivudine 100 mg/day Duration: One year	Primary endpoint: Median reductions of HBV DNA levels at week 52 Patients: - HBeAg-positive adults with compensated chronic hepatitis B - Baseline ALT 1.3-10 X upper limit of normal (ULN), HBV DNA > 6 $\log_{10}$ - Age 18-65 years - Mostly Asian (80-90%)	- Results ($\log_{10}$ copies/mL reductions): Telbivudine 400 mg 6.43; Telbivudine 600 mg 6.09, Combo 400 mg 6.40; Combo 600mg 6.05; Lamivudine 4.66 ($P < 0.05$ for telbivudine monotherapy vs lamivudine monotherapy) - At week 52 telbivudine monotherapy showed significantly greater mean reduction in HBV DNA levels and more normalization of ALT (86% vs 63%; $P < 0.05$) than lamivudine monotherapy. - HBeAg seroconversion: telbivudine monotherapy 31%, lamivudine monotherapy 22% (difference was not statistically significant) -No synergistic effect in combination therapy. Combination therapy was not better than telbivudine monotherapy. -All treatments were well tolerated
Bzowej N, et al. (2006)[8]	GLOBE trial is a 2-year, Phase III, randomized clinical study that is enrolling patients from the > 20 countries worldwide. (N = 921 HBeAg-positive patients; N = 446 HBeAg-negative patients) Treatment Groups 1) Telbivudine 600 mg daily 2) Lamivudine 100 mg daily Duration: up to 2 years.	Primary endpoint was not specified, but outcome measures included decrease in $\log_{10}$ HBV DNA (COBAS PCR assay), % Histologic response, ALT normalization, % therapeutic response (HBV DNA < 5 $\log_{10}$ + ALT normalization or HBeAg loss), % HBeAg loss, and % HBV resistance. Patients: - Compensated liver disease, baseline ALT 1.3-10 X upper limit of normal (ULN), HBV DNA > 6 $\log_{10}$ $P > 0.01$	**- Week 52 (HBeAg (positive))** • Decrease in $\log_{10}$ HBV DNA: telbivudine 6.5, lamivudine 5.5[a] • % Histologic response: 65% telbivudine vs 56% lamivudine[a] • %ALT normalized: 77% telbivudine, 75% lamivudine • % Therapeutic response: 75% telbivudine vs. 67% lamivudine[a] • % HBeAg loss: 26% telbivudine, 23% lamivudine • % HBV resistance: 3% telbivudine vs 8% lamivudine[a] **- Week 52 (HBeAg (negative))** • Decrease in log10 HBV DNA: telbivudine 5.2, lamivudine 4.4[a] • % Histologic response: 67% telbivudine vs. 66% lamivudine • %ALT normalized: 74% telbivudine, 79% lamivudine • % Therapeutic response: 75% telbivudine vs 77% lamivudine • % HBV resistance: 2% telbivudine vs 9% lamivudine[a] **-Week 76 (HBeAg (positive))** • Decrease in $\log_{10}$ HBV DNA: telbivudine 6.6, lamivudine 5.2[a] • %ALT normalized: 78% telbivudine, 68% lamivudine[a] • % Therapeutic response: 75% telbivudine vs 58% lamivudine[a] • % HBeAg loss: 40% telbivudine, 26% lamivudine[a] **-Week 76 (HBeAg (negative))** • Decrease in log10 HBV DNA: telbivudine 5.3, lamivudine 4.7 • %ALT normalized: 76% telbivudine, 64% lamivudine • % Therapeutic response: 75% telbivudine vs 70% lamivudine
Heathcote E et al. (2006)[9]	Multicenter, randomized (2:1), open-label international study (N = 135) **Drugs:** Adefovir 10mg daily Telbivudine 600mg daily At week 24, 50% of patients in adefovir arm were randomly assigned to switch to telbivudine. Treatment will continue for a total of 52 weeks.	Primary Outcome: HBV DNA reduction at week 24 Patients: - HBeAg-positive chronic hepatitis B, previously untreated - HBV DNA >6 $\log_{10}$ copies/mL - ALT levels 1.3-10 X ULN - Compensated liver disease - 75% male, 15% female - 90% Caucasian	- At week 24, telbivudine was superior to adefovir at HBV DNA reduction (6.30 vs. 4.97; $P < 0.01$) - Treatment failure (not achieving HBV DNA< 5 $\log_{10}$ copies/mL) was lower in the telbivudine group than adefovir (5% vs 42%; $P < 0.01$) - ALT (61-62%) and loss of HBeAg (10-16%) were similar in both arms - Both treatments were well tolerated with similar rates of adverse events

treated patients after 24 weeks of therapy.[9] In addition, telbivudine has not been studied in patients with decompensated liver disease, or in lamivudine-, entecavir-, and adefovir-resistant patients.[3] Table 4 summarizes the results from clinical trials that evaluated the efficacy of telbivudine in the management of chronic HBV infection.

Conclusion

There is a crucial need for the development of new, well-tolerated agents that are effective for the management of chronic HBV patients, as resistance to certain medications has emerged in recent years. Currently, 4 oral agents, telbivudine, entecavir, adefovir dipivoxil, and lamivudine are available for use in the treatment of chronic HBV infections. Telbivudine has not been studied in patients with decompensated liver disease, whereas adefovir represents the best-studied agent in patients with compensated/decompensated cirrhosis patients.[1,5] In addition, the efficacy of telbivudine in the treatment of adefovir-, entecavir-, and lamivudine-resistant chronic HBV patients has not been established. Recent studies have confirmed the superior efficacy of telbivudine compared with that of lamivudine in regards to DNA reduction, proportion of patients achieving ALT normalization, and the rate of HBeAg loss in HBeAg (+) patients. The clinical efficacy of telbivudine is less convincing in HBeAg (-) patients, as no difference in efficacy was found between telbivudine and lamivudine after 76 weeks of therapy. In contrast, entecavir has been shown to be superior to lamivudine in reducing HBV DNA levels and in normalizing ALT levels in HBeAg (-) patients and in HBeAg (+) patients. Although early results from clinical trials are promising, future clinical trials will help further define the potential role of telbivudine in the management of chronic HBV patients. ■

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CME Questions

22. All of the following measures are recommended by the CDC at the time of central catheter insertion except:

a. Hand washing/sanitizing
b. Application of mupirocin to the catheter insertion site
c. Use of chlorhexidine for skin preparation
d. Avoidance of insertion into the femoral vein
e. Full barrier precautions.

23. Which of the following is correct?

a. Male sexual partners of women with vaginal trichomoniasis are rarely infected with this Trichomonas vaginalis.
b. The majority of trichomonas infections in men are asymptomatic.
c. Trichomonas vaginalis is a flagellated fungus.
d. Posaconazole is an effective alternative treatment for vaginal trichomoniasis.

24. Which of the following is correct?

a. Telbivudine inhibits hepatitis C viral protease.
b. Telbivudine is a thymidine nucleoside analog reverse transcriptase inhibitor approved for the treatment of HIV infection.
c. Four agents are approved in the U.S. for the treatment of chronic hepatitis B virus infection: lamivudine, entecavir, adefovir, and telbivudine.
d. The major toxicity of telbivudine is renal.

Answers: 22.(b) 23.(b) 24.(c)

Corrections

Please note the following corrections. We apologize for any confusion or difficulty these mistakes may have caused.

1. Last month's issue was incorrectly numbered; it should have been Volume 26, Number 4, pages 37-48; CME questions should have been numbered 19-21.

2. Last month's CME question number 2 was mistakenly printed in the issue. The article that corresponds to that question was not run.

3. In September 2006, Christine Maddox's name was mistakenly attributed to the article "Update on Quinolone-Induced Changes in Glycemic Control"; she is the co-author of the article published in the September issue of *Infectious Disease Alert* entitled "Myopathy Associated with Daptomycin Use." ■

In Future Issues:

Is viral culture of cerebrospinal fluid (CSF) obsolete?

UPDATES

By Carol A. Kemper, MD, FACP

Resistant Salmonella from Pet Rodents

Source: Swanson SJ, et al. Multidrug resistant *Salmonella enterica* Serotype Typhimurium associated with Pet Rodents. *N Engl J Med*. 2007;356:21-28.

An outbreak of highly drug-resistant *S. enterica* Serotype Typhimurium — which was resistant to all drugs tested — was first identified in 2 young boys in 2004 in Minnesota and North Carolina who had been in contact with pet mice. These events prompted further investigation, and ultimately, a total of 28 cases with matching *S. enterica* isolates were identified in 10 states. Twenty-two available patients were interviewed, including 13 children and adults with exposure to pet hamsters, mice or rats, 2 (9%) with secondary exposure, and 7 patients without documented rodent exposure. Forty percent required hospitalization, higher than generally expected with Salmonella infection, but common with drug-resistant isolates. Susceptibility studies showed resistance to ampicillin, sulfisoxazole, tetracycline, streptomycin and chloramphenicol.

Shortly after being purchased, many of the pet rodents became ill with diarrhea and lethargy, and, in the Minnesota case, a young 5-year old boy cradled his dying mouse only one week after receiving it as a gift, and shortly before becoming ill himself.

Investigation revealed identical isolates (*S. enterica* serotype Typhimurium phage type 120) in pet rodents from 13 different pet stores, supplied by 7 different distributors, in 10 different states. The organism was also isolated from pet cages and reusable transport cartons. Salmonella can survive from more than one year in the environment. Even exposure to reusable contaminated transport bins could risk infection of an entire population of rodents being shipped for sale. In addition, the stress associated with transport may lead to reactivation of *S. enterica* in animals, resulting in increased diarrhea and bacterial shedding.

Four different breeders or distributors were found to routinely administer antimicrobials for non-specific diarrheal symptoms in animals. In addition, investigators found that tetracycline was routinely used in feed, and that rodents received antimicrobials in their drinking water at weaning, and before and after transport. This undoubtedly contributed to the broad resistance of these organisms.

Stricter infection-control practices should be implemented for the sale and distribution of pet rodents. Parents should be appraised of the risks of illness in purchased pets, and instructed as to good cage hygiene and handling of animals with special attention to hand cleansing. ■

Decolonization of MRSA is Effective

Source: Simor AE, et al. Randomized controlled trial of chlorhexidine gluconate for washing, intranasal mupirocin, and rifampin and doxycycline versus no treatment for the eradication of methicillin-resistant Staphylococcus aureus colonization. *CID*. 2007;44:178-185.

It is estimated that at least 2,000,000-3,000,000 people in the United States are colonized with MRSA. While aggressive decolonization and work-restriction policies have been utilized in some European countries, attempts at decolonization have not been endorsed by health agencies in the United States. Fears of emerging resistance, toxicity, expense, and a lack of data demonstrating durable effectiveness have diminished interest in routine decolonization of individuals colonized with MRSA. And yet, an increasing amount of data indicates that colonization with MRSA results in an increased risk of bacteremia, surgical wound infection, and other infectious complications in hospitalized patients.

For this reason, Simor and colleagues' data is welcome information. A total of 146 patients were enrolled in a randomized (3:1) controlled trial of systemic and topical antimicrobial treatment (topical chlorhexidine gluconate body scrubs, topical mupirocin, and combination oral rifampin and doxycycline for 7 days) vs no treatment. To enroll, patients had to have positive MRSA cultures from one or more body sites on 2 occasions within a 2-week interval. Prior treatment specific for MRSA was acceptable but previous attempts at decolonization were not. Follow-up cultures of nares, perineum, skin lesions, catheter exit sites, and previous sites of infection were obtained monthly for up to 8 months. The primary study endpoint was clearance of all sites at 3 months post-treatment.

Remarkably, 64 (74%) of patients in the treatment group had negative follow-up cultures at 3 months, compared with only 8 (32%) in the non-

treatment group (P = 0.0003). A Kaplan-Meier colonization-free survival curve demonstrated a significant decrease in colonization over time in the treated group (P < 0.0001). In those with positive cultures at 3 months post-treatment, 82% were colonized with the same organism, as identified by PFGE typing, but 18% had differing isolates. Given the high frequency of certain MRSA organisms circulating in long-term care facilities or hospitals, it may not be possible to determine if a patient was successfully decolonized but then re-colonized from an outside source with an identical organism.

Persistence of MRSA occurred in 60% of patients with high-level mupirocin resistance. High-level mupirocin resistance, identified in 19% of isolates, was the major risk factor leading to failure of the regimen but, surprisingly, impaired functional status and the presence of open wounds or medical devices was not. The significance of low-level mupirocin resistance, found in 5%, could not be assessed given its low frequency. However, a worrisome finding of this study was the emergence of high-level resistance to mupirocin in 5% of treated patients during study.

Interestingly, none of the isolates proved to be USA300, the most common community acquired MRSA isolate in our area in Northern California. The most common strains identified were CMRSA-2 in 46% (similar to USA100 ST5), and CMRSA-1 in 24% (USA 600 ST4.5).

Combinations of systemic and topical antimicrobials are safe and effective in eradicating MRSA in a majority of colonized patients. Given the high frequency of failure in those with pre-existing mupirocin resistance, testing for mupirocin resistance before attempting decolonization would seem appropriate. Commercial testing is now available through some laboratories. ■

Sensitivity of Interferon Assay in Active TB

Source: Dewan PK, et al. Low sensitivity of a whole-blood interferon-gamma release assay for detection of active tuberculosis. *CID*. 2007; 44:69-73.

New tests based on the gamma interferon immune response to *M. tuberculosis* have many potential benefits over standard TST skin testing in the detection of latent TB. Such assays have a high degree of specificity in clinical trials (99.8%), which eliminates the need for 2-step skin testing, and decreases health care personnel time and office visits. In addition, previous BCG vaccination does not interfere with these assays. One of these products, the Quantiferon-TB Gold assay (QFT-G, Cellestis), has been approved for use in the United States and is already being broadly utilized for screening of health care workers. A limitation of these assays is the diminished sensitivity in patients with T-cell dysfunction. And, the assay cannot distinguish between latent and active disease.

These authors at the San Francisco public health department evaluated the utility of interferon-gamma assay in the assessment of persons with suspected TB. A total of 442 subjects with suspected or documented TB were identified through a review of clinical records in 2005, 242 (55%) of whom were tested using the QFT-G assay. Of these, 45(19%) were diagnosed with TB, 37(82%) of whom were confirmed by culture. In patients diagnosed with active TB, QFT-G results were positive in 55%, negative in 38%, and indeterminate in 7% (overall sensitivity 60% for this group, with a negative predictive value of 86%). A similar sensitivity (64%) was observed for those with culture-confirmed disease.

Interestingly, patients with extra-pulmonary disease were more likely to have a false-negative result compared with those with pulmonary disease (35% vs 4%, P < 0.05). The timing of the testing or duration of therapy did not appear to affect the results.

Of those 45 patients diagnosed with TB, 24 had paired skin TST test and QFT-G results. Both test were positive in 50%, both tests were negative in 4%, 38% had positive skin testing and a negative QFT-G result, and 8% had negative skin testing and an indeterminate QFT-G results. No patient diagnosed with TB had a negative skin test and a positive interferon assay test result.

Only 3 patients with HIV were diagnosed with TB; QFT-G results were positive, negative and indeterminate in one patient each.

The QFT-G assay, while very helpful in the recognition of patients with latent TB, has a diminished sensitivity (60%) in patients with active TB disease. Clinicians should be mindful that a negative interferon-gamma assay does not rule-out TB, similar to the experience with skin testing.

On a similar note, clinicians are inquiring whether patients with latent disease based on TST findings (some of whom may have had BCG vaccination in the past) can stop their treatment for latent TB based on a negative QFT-G result. Until such time as data exists to define the sensitivity of the assay in a partially treated population, patients should continue their ongoing treatment based on current public health recommendations. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

This Month's Issue Focuses on Women's Health

Breast Cancer Rates Have Dropped Since WHI of 2002

Several important papers have been published in the last 2 months, none more important than the realization that breast cancer rates have dropped precipitously since the publication of the Women's Health Initiative (WHI) in 2002. The issue of estrogen-alone (not in combination with a progestin) and the risk of breast cancer is addressed in a new paper, as is the use of herbal supplements to treat postmenopausal vasomotor symptoms in women who have stopped HRT. Finally the duration of treatment of bisphosphonates for osteoporosis gains some clarity with publication of new data from the Fracture Intervention Trial.

The WHI study of combined estrogen and progesterone was halted in 2002 when it was found that women on the drug combination were at increased risk of breast cancer. Prior to the publication of the study, it was estimated that 30% of American women over the age of 50 were taking HRT. Within 6 months of the publication of WHI, half of those women had discontinued HRT. Now preliminary data suggests that breast cancer rates dropped precipitously in 2003 compared to 2002. The decline was most pronounced in women over the age of 50, and the biggest decline was in estrogen-receptor-positive breast cancer. Breast cancer rates had been rising steadily in this country at an average of 1.7% per year until 1998 when the rate began declining at 1% per year. The 7% drop seen in 2003 was the largest single decrease ever seen within a single year. The data was presented at the 29th Annual San Antonio Breast Cancer Symposium by researchers from MD Anderson. In a separate study, researchers from Northern California presented their own data that showed a decrease in hormone use of 68% between 2001 and 2003, and a decrease in breast cancer rates of 10-11%, which was sustained to 2004 (*J Clin Oncology* 2006;24:e49-50). The implication is that the sudden decrease in HRT use is responsible for the decrease rate of breast cancer, a conclusion supported by the dramatic decrease in ER positive cancers in postmenopausal women.

In contrast to the findings of the estrogens/progesterone wing of the Women's Health Initiative, the estrogen-only wing showed no increased risk of breast cancer (*JAMA*. 2004;291:1701-12). This was in contrast to several European studies, including the Million Woman Study, which showed an increased rate of breast cancer with unopposed estrogen (*Lancet*. 2003;362:419-427). Now a new study also suggests that estrogen-only is associated with a slightly increased risk of breast cancer. The study from Finland looked at nearly 85,000 women using oral or transdermal estradiol, 8,000 women using oral estriol (widely used in Europe but uncommonly used in the United States), and 18,000 women using vaginal estrogens for least 6 months were followed from 1994 through 2001. There was no increase risk for breast cancer for estradiol use of less than 5 years. Women who used estradiol for more than 5 years had a relative risk of breast cancer of 1.44 (1.29-1.59). Oral and transdermal estradiol conveyed similar risk. Oral estriol and vaginal estrogens did not increase breast cancer risk. The authors con-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. 'In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

clude that the use of estradiol for more than 5 years is associated with a increased risk of breast cancer (*Obstet and Gynecol*. 2006;108:1354-1360).

Herbal Supplements to Treat Vasomotor Symptoms

Many women who have stopped HRT have tried herbal supplements to treat vasomotor symptoms. A new study compares the effectiveness of black cohosh, multibotanicals, and soy with HRT and placebo. Researchers from the University of Washington enrolled 351 women who were in menopausal transition or were postmenopausal. They were given black cohosh 160 mg daily, multibotanical with black cohosh 200 mg plus 9 other ingredients, multibotanical plus dietary soy counseling, HRT with conjugated equine estrogen 0.625 mg daily with or without medroxyprogesterone 2.5 mg daily, or placebo. There was no difference in vasomotor symptoms between the herbal interventions and placebo at 3, 6, or 12 months or for the average over-all follow-up time points ($P > 0.05$ for all comparisons), with the exception that symptom intensity was significantly worse with the multibotanical plus soy compared with placebo ($P = 0.016$). Hormone therapy was effective at reducing vasomotor symptoms ($P < 0.001$). The authors conclude that black cohosh alone or as part of a multibotanical regimen was ineffective at treating menopausal vasomotor symptoms (*Ann Int Med*. 2006; 145: 869-879). As pointed out in an accompanying editorial, even though herbal supplements were found to be ineffective, the good news is that women in the placebo group had a 30% reduction in the severity and frequency of vasomotor symptoms during the 12-month follow up, a number that probably reflects the natural history of postmenopausal symptoms (*Ann Int Med*. 2006;145:924-925).

Bisphosphonates to Treat LBD, After 5 Years?

Since WHI, bisphosphonates have become the drugs of choice for many women with low bone density. Treatment with bisphosphonates for 5 years is safe and effective; however, treatment beyond 5 years has been debated with some experts recommending a "drug holiday" after 5 years because of a concern about diminished bone strength and microfractures. A new study suggests that there is no harm in extending treatment beyond 5 years, although there is minimal benefit. In the Fracture Intervention Trial (FIT), 1,099 postmenopausal women who had used alendronate for 5 years were randomized to 5 more years of alendronate 5 mg per day, 10 mg per day, or placebo. Outcomes were hip bone mineral density (BMD) with an exploratory outcome measure of fracture incidence. Compared to women who continued alendronate, those who were switched to placebo at 5 years had declines in BMD at the total hip (-2.4%; 95% CI, -2.9% to -1.8%; $P < 0.001$) and spine (-3.7%; 95% CI, -4.5% to -3.0%; $P < 0.001$). Still, despite discontinuing alendronate, BMD remained at levels above pretreatment levels 10 years earlier. The cumulative risk for non-vertebral fractures was not significantly different between those continuing or discontinuing alendronate (19% vs 18.9%). Those who continued alendronate had significant lower risk of clinically recognized vertebral fractures, however, (5.3% placebo vs 2.4% alendronate) but no significant reduction in morphometric vertebral fractures. Of the women continuing alendronate, 18 underwent bone biopsies and none showed any qualitative abnormalities. The authors conclude that discontinuing alendronate after 5 years results in a moderate decline in BMD, a gradual rise in biochemical markers, but no higher fracture risk other than for clinical vertebral fractures compared to women who continued alendronate. The data also suggests that stopping alendronate at 5 years is safe, although the authors suggest that high-risk women may want to continue beyond 5 years (*JAMA*. 2006;296:2947-2953). Interestingly, no cases of osteonecrosis of the jaw were reported in women who took alendronate for 10 years.

FDA Actions

The FDA has approved a new estradiol gel for the treatment of moderate to severe vasomotor symptoms assisted with menopause. The gel, which is applied daily, supplies the lowest dose of estradiol approved by the FDA for this indication. Estradiol gel will be marketed as "Elestrin" by Kenwood Therapeutics.

The FDA has approved Novartis' combination antihypertensive "Exforge." The drug combines valsartan and amlodipine in one pill that is dosed once daily. It is expected to be marketed by September 2007.

The FDA has approved the first generic ondansetron injection (Zofran) for the prophylaxis of postoperative nausea and vomiting, and nausea and vomiting associated with cancer chemotherapy. The generic is manufactured by Teva pharmaceuticals.

The FDA has also approved generic oxybutynin extended release tablets (Ditropan XL). 'The new generics will be available in 5 mg and 10 mg extended-release tablets made by Mylan, and 50 mg extended-release tablets manufactured by Impax Laboratories. Oxybutynin is indicated for once daily treatment of overactive bladder in patients with urge incontinence, urgency, and frequency.

A generic bupropion extended-release tablet has been approved by the FDA. The generic version of Wellbutrin XL for the treatment of depression will be available in 150 mg and 300 mg tablets. The new generic is manufactured by Anchen Pharmaceuticals. ■