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INSIDE

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Darunavir (TMC114) Approved by the FDA

SPECIAL FEATURE

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 is on the speaker's bureau for GlaxoSmithKline and Pfizer.

DARUNAVIR (KNOWN DURING DEVELOPMENT AS TMC114 AND given the proprietary name, PREZISTA-TM) was approved by FDA on June 23, 2006, for use in combination with other antiretroviral agents for the treatment of HIV infection in adults.[1] Darunavir is currently labeled for use only in treatment-experienced adults at the present time, since the clinical trials submitted to FDA to date were limited to this patient population.[2] It is administered with low-dose ritonavir. Adult dosing is generally darunavir 600 mg/ritonavir 100 mg administered b.i.d.

Chemistry: Darunavir's nonpeptidic protease inhibitor (PI), has a molecular weight of 593.73, and is a sulfonamide isostere. Isosteres are compounds that have the same number of valence electrons and in the same configuration, but differing in the kinds and numbers of atoms. It is supplied as a 300 mg tablet formulation.

Preclinical toxicology: Reproduction studies show no embryotoxicity in mice, rats, or rabbits. However, darunavir is FDA Pregnancy Category B since no adequate and well-controlled studies have been conducted in pregnant women.

Human Pharmacology: Darunavir has absolute bioavailability of 37% after single-dose administration of 600 mg, and bioavailability increases to 82% when administered with ritonavir. T_{max} is reached at 2.5-4 hours, and AUC is approximately 30% higher when administered with food. Darunavir is approximately 95% protein bound, and binding is primarily to alpha-1-acid glycoprotein. Darunavir undergoes oxidative metabolism by the cytochrome P450 system, mainly via the CYP3A iso-

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form. A mass balance study in healthy volunteers showed 79.5% and 13.9% of C14-labeled darunavir recovered in the stool and urine, respectively. No data exist on the use of darunavir in patients with varying degrees of hepatic impairment; therefore, the package insert advises caution when using in patients with liver disease. The package insert provides numerous tables showing various drug interactions. In view of darunavir's known route of metabolism, as well as the need to co-administer darunavir with ritonavir, the usual boosted PI drug interactions and precautions apply.

Preclinical Microbiology: Darunavir has potent in vitro activity against wild type HIV, with EC50 ranging from < 0.1-4.3 nM. Darunavir-resistant virus selected in vitro from wild type HIV-1 showed 6- to 21-fold decreased susceptibility to darunavir and contained 3-6 of the following substitutions in protease: S37N/D, R41E/S/T, K55Q, K70E, A71T, T74S, V77I, or I85V. Numerous additional amino acid substitutions (most often L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V) were seen when HIV strains, with pre-existing PI resistance, were passed serially in vitro with darunavir, and virus containing at least 8 substitutions exhibited 50- to 641-fold reduced susceptibility to darunavir.

Clinical Efficacy: FDA approval was based on pooled analysis of treatment-experienced adult patients from 2 randomized, controlled trials of optimized best regimen (OBR) plus darunavir/r vs OBR plus an investigator-selected comparator PI. Patients in these trials had HIV-1 RNA > 1000 copies/mL, had prior PI treatment, and had at least one primary PI substitution (D30N, M46I/L, G48V, I50L/V, V82A/F/S/T, I84V, L90M) at screening. The primary analysis was conducted at 24 weeks, and demonstrated that 45% vs 12.1% of patients had HIV RNA levels of < 50 copies/mL in the darunavir vs comparator PI arms.

Baseline Genotype/Phenotype and Virologic Outcome Analyses: Baseline substitutions V32I, I47V, or I54L/M were associated with decreased virologic response in vivo. In addition, diminished virologic response was observed in patients with ≥ 7 PI substitutions at 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, or 90. Additional analyses suggested that presence at baseline of 3 or more of the following substitutions was associated with decreased virologic response: V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, or L89V. Response was proportionately less as the number of these substitutions present at baseline was greater. (It should be noted that these data simply report observed associations and include both true resistance-producing substitutions and compensatory substitutions. Sorting out which of these are truly important from a mechanistic standpoint will require time-intensive experiments using site directed mutagenesis, where specific mutations and combinations are engineered into an infectious molecular clone of HIV.) When the sponsor looked at baseline phenotypic susceptibility to darunavir (using shift in IC50 compared to a reference standard), patients with baseline susceptibility of 0-2X had 60% achieved HIV RNA < 50 copies/mL at week 24; >2-7X (47%), >7-30X (24%), and >30X (18%).

Cross-resistance: Since darunavir is currently restricted for use in treatment-experienced patients, concern about proper sequencing of darunavir vs tipranavir is of obvious interest to clinicians. Darunavir has < 10X decreased susceptibility in cell culture against 90% of 3309 clinical isolates of HIV-1 resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir. While darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir in cell culture, 6 or 9 darunavir-resistant viruses selected in cell culture retained in vitro susceptibility to tipranavir. Of the viruses isolated from patients expe-

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Questions & Comments

Leslie Hamlin,
Associate Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

riencing virologic failure on darunavir/ritonavir in the clinical trials, > 50% retained in vitro susceptibility to tipranavir while < 5% were susceptible to other PIs. These data suggest that a significant proportion of individuals failing therapy with tipranavir could experience a good virologic response in vivo to darunavir, and imply that at least some patients who fail darunavir could still respond to tipranavir.

Adverse Reactions: Gastrointestinal side effects of darunavir were similar to the comparator PI arm in the controlled trials. Elevations in transaminases appeared to be slightly less frequent with darunavir than with the comparator PI. Hematologic effects of darunavir were comparable to the comparator PI. Hypertriglyceridemia was comparable to the control arm. Grade 2-4 hypercholesterolemia was seen more frequently in the darunavir arm than in the comparator arm (9.2% vs 3.3%); however, the high frequency of hyperbilirubinemia in the comparator arm suggests that atazanavir was frequently used as the comparator PI, and it is known that atazanavir causes less frequent hyperlipidemia than other commonly used PIs.

Summary: Darunavir represents an important addition to our antiretroviral armamentarium. It is active in vivo in patients who have PI-resistant virus, and preliminary cross-resistance data suggest that darunavir may retain utility in patients who develop virologic failure on tipranavir. However, despite the promising in vitro data, it should be noted that in the patients who had more than 7 substitutions in protease at baseline, only 14% of darunavir-treated patients sustained HIV RNA levels of < 50 copies/mL at week 24. This emphasizes the importance of drug resistance testing prior to treating a patient with darunavir, aggressive construction of an optimized background regimen and, by extrapolation from studies of tipranavir, strong consideration to including enfuvirtide in the regimen. Darunavir's precise role in salvage therapy awaits further controlled trials, including head to head comparisons with tipranavir. The safety profile of darunavir/ritonavir is acceptable, and appears better tolerated than tipranavir/ritonavir, particularly with regard to hepatotoxicity. ■

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CDAD: Novel Therapeutics

ABSTRACTS & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Both nitazoxanide and the investigational anionic polymer, tolevamer, may have efficacy comparable to that of standard therapies in the treatment of CDAD. The addition of rifampin to metronidazole is not superior to treatment with metronidazole alone.*

Sources: Louie TJ, et al Tolevamer, a Novel Nonantibiotic Polymer, Compared with Vancomycin in the Treatment of Mild to Moderately Severe *Clostridium difficile*-Associated Diarrhea. *Clin Infect Dis*. 2006;43:411-420; Musher DM, et al. Nitazoxanide for the Treatment of *Clostridium difficile* Colitis. *Clin Infect Dis*. 2006;43:421-427; Lagrotteria D, et al. Prospective, Randomized Inpatient Study of Oral Metronidazole Versus Oral Metronidazole and Rifampin for Treatment of Primary Episode of *Clostridium difficile*-Associated Diarrhea. *Clin Infect Dis*. 2006;43:547-552.

LAGROTTERIA AND COLLEAGUES ENROLLED 39 INpatients with a primary episode of *Clostridium difficile*-associated diarrhea (CDAD) to receive treatment for 10 days with either metronidazole (MET) alone or together with rifampin (RIF). This single-blind study was prematurely discontinued prior to enrolling the planned 100 patients because of loss of funding. Nonetheless, the results were consistent with a lack of benefit from the addition of rifampin to metronidazole. Thus, 65% of MET and 63% of RIF/MET recipients had improved by day 10, and the proportion who relapsed was also similar in the 2 treatment arms.

Louie and colleagues randomized 289 patients with either primary or recrudescent CDAD to treatment with vancomycin for 10 days, or to tolevamer at one of 2 total daily doses (3 g or 6 g) for 14 days. The trial was double-blind. Diarrhea resolved in 91% of vancomycin recipients after a median duration of 2.0 days, in 67% of recipients of 3 grams of tolevamer after a median of 4.0 days, and in 83% of those receiving 6 grams of tolevamer daily after a median of 2.5 days. The 6 gram tolevamer regimen was non-inferior to vancomycin with regard to the primary end point of the study and the time to resolution of diarrhea. The recurrence rates for the 2 treatment arms were 10% for tolevamer and 19% for vancomycin ($P = .19$).

In a prospective, double-blind trial, Musher and colleagues randomized 142 patients with CDAD to treatment with either metronidazole for 10 days or to

nitazoxanide (total of 1 gram daily) for either 7 or 10 days. The response rates in the 3 treatment arms were similar (82.4%, 90.0%, and 88.9%, respectively). There, subsequently, were 4 documented recurrences of CDAD in the metronidazole recipients, 9 in those who received nitazoxanide for 7 days, and 4 in those who received the latter for 7 days. Thus nitazoxanide therapy was not inferior to treatment with metronidazole.

COMMENTARY

The increasing incidence of CDAD, together with the emergence of an epidemic strain (ribotype 029, toxinotype III, NAP-1) of apparently increased virulence, and a perceived reduction in the efficacy of standard therapies, with a possibly increased incidence of recrudescence after treatment, has placed a sharp focus on this disease. Given the seriousness of the problem, together with the volume of words written regarding recommendations for treatment, the amount of quality evidence on which to base therapeutic decisions is remarkably limited. As a result, studies such as the above are welcome.

There have previously been a number of anecdotal reports leading to some recommendations for the addition of rifampin to metronidazole in the treatment of CDAD. The study reviewed here, although quite underpowered, suggests that, at least in primary infection, this strategy does not provide benefit over that seen with the use of metronidazole alone.

Tolevamer is an investigational anion exchange resin without antimicrobial activity that has been demonstrated to neutralize, presumably by binding toxins A and B of *C. difficile* in an animal model. Cholestyramine has previously been used for this purpose, but clinical evidence for its efficacy is lacking. The study by Lagrotteria and colleagues suggest that this newer anionic polymer has efficacy similar to that of vancomycin in patients with CDAD, approximately three-fourths of whom had primary disease. In addition, since a dose response to tolevemar was observed, it is possible that total daily doses, in excess of 6 grams, may be even more effective.

Nitazoxanide is US FDA-approved for the treatment of giardiasis and cryptosporidiosis, and has in vitro activity against *C. difficile* at concentrations well below those achieved in the colon after oral administration. The work by Musher et al suggest that its efficacy is similar to that of metronidazole. Nitazoxanide is, however, much more expensive than metronidazole.

A comparison of the results of metronidazole therapy in the 2 trials that utilized this as the standard therapy, indicate the danger of comparing results across trials. The reported response rate to metronidazole given alone in the study by Largoretta et al was only 65%, while it was 82.4% in the study by Musher et al. This difference could be due to varying severity of illness, differing end point definitions, and the like.

While these studies report varying incidences of recrudescent disease, none performed the molecular epidemiologic studies necessary to distinguish relapse from reinfection.

A number of additional agents are being investigated for treatment of CDAD, including the lipoglycodepsipeptide, ramoplanin, the rifamycin, rifaximin, and the benzoxazinorifamycin, rifalazil. Others under investigation include OPT-80 (tiacumicin B), an 18-membered macrocyclic nonabsorbable antibiotic, as well as monoclonal antibodies that neutralize toxins A and B. Perhaps, of most significance (if it works), is that a toxoid vaccine has entered early trials. ■

Preventing Fungal Infection: Does Clean Air Matter?

ABSTRACT & COMMENTARY

By J. Peter Donnelly, PhD

Clinical Microbiologist, University Hospital, Nijmegen, The Netherlands

Dr. Donnelly is a consultant for Ortho Biotech, and does research for Janssen, Merck, Novartis, Numico, Pharmacia, and Pfizer.

Synopsis: *Systematic review of 16 studies showed HEPA filtration appeared to help reduce the incidence, but did not influence mortality, of fungal infections among patients treated for acute leukemia or receiving a haematopoietic stem cell transplant.*

Source: Eckmanns T, et al. The Influence of High-Efficiency Particulate Air Filtration on Mortality and Fungal Infection Among Highly Immunosuppressed Patients: A Systematic Review. *J Infect Dis*. 2006;193:1408-1418.

It is widely accepted that vulnerable patients are best protected from acquiring invasive mold diseases by placing them in a protected environment, supplying sterile air by means of HEPA filtration

Figure 1

Comparison of protected environment HEPA/LAF with no ventilation — impact on invasive fungal diseases

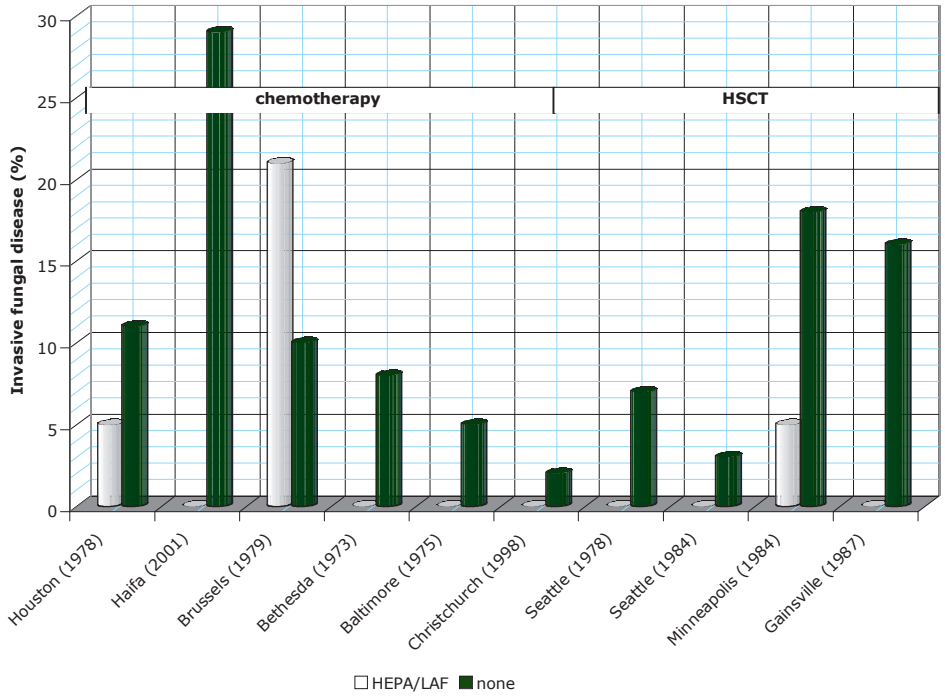
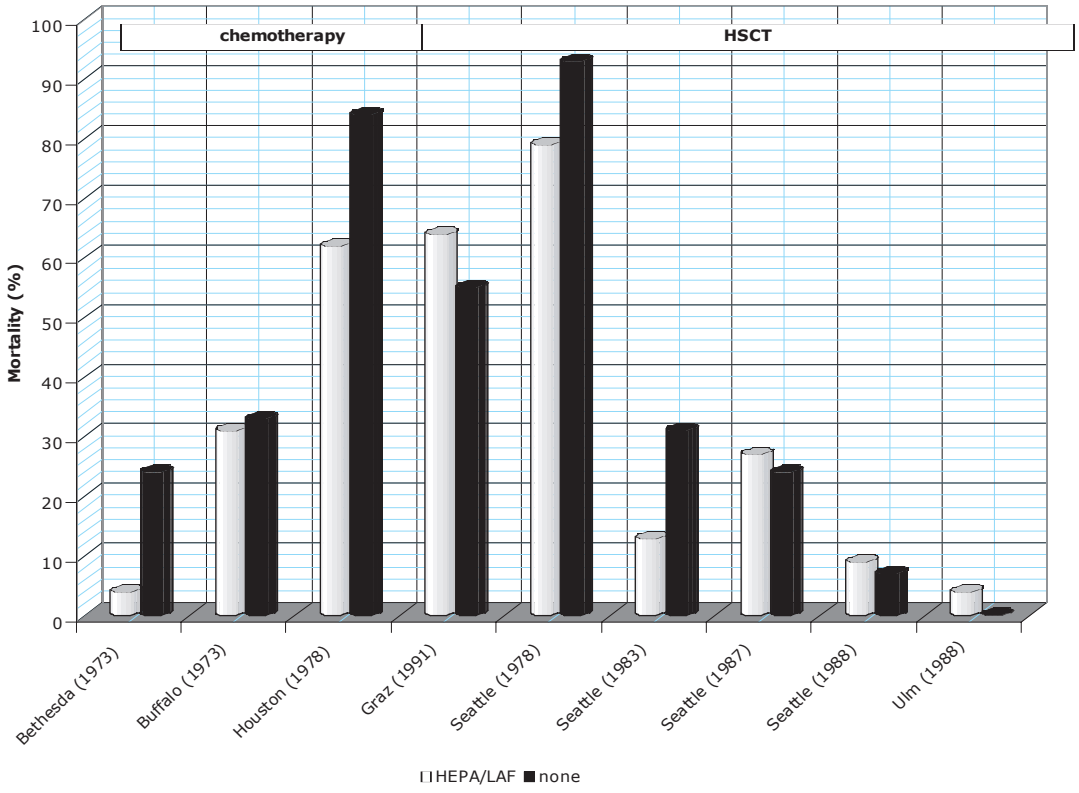


Figure 2

Comparison of protected environment HEPA/LAF with no ventilation — impact on mortality



with or without laminar air flow (LAF). However, there is little to support this contention. To rectify this, Eckmanns and colleagues undertook a meta-analysis of studies in this area. They found only 16 formal trials of this type of protected environment involving nearly 1000 subjects. These had been admitted to 7 centers in the United States, and 5 elsewhere, for an HSCT or for chemotherapy of acute leukemia. Each study was scrutinized, and the data were subjected to meta-analysis to evaluate the efficacy of this measure in lowering the occurrence of invasive fungal diseases and mortality. Only 8 studies were randomized, controlled trials (RCT), and only 3 reported on both measures. While there was a reduction in the incidence of invasive fungal disease in 9 of the 10 studies that reported these data (*see Figure 1*), the difference was only significant for the 4 that were RCTs. HEPA filtration/LAF led to reduced mortality in 5 of 9 studies (*see Figure 2*), but did not significantly reduced the relative risk of death among neutropenic patients treated for hematological malignancies, whether the studies were randomized, controlled trials (8 studies; RR = 0.86, 95%; CI = 0.65-1.14) or not (8 studies, RR = 0.87, 95%; CI = 0.60-1.25). So whilst employing HEPA/LAF appears beneficial, unequivocal evidence to support this type of facility is still waiting to be gathered.

COMMENTARY

The question of whether or not HEPA filtration/LAF should be used to create a protected environment for patients at risk of developing invasive fungal diseases — namely being treated for cancer and are receiving hematopoietic stem cell and solid organ transplants — is a real and an expensive one. Most centers dealing with these patients push hard for the best facilities supplied with HEPA filtered air to keep out fungal spores. On the face of it, this is not unreasonable, as the air is loaded with the very fungal spores that are inhaled by the patients that lead to invasive fungal diseases. Also, common sense dictates that if the air is the bearer of deadly spores, then patients ought to be protected while they are at their most vulnerable (ie, in hospital for intensive chemotherapy, with or without radiation therapy, for cancer or to prepare for an HSCT). Moreover, the experts who drafted the CDC/IDSA guidelines (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr410a1.htm) strongly recommend "All allogeneic recipients should be placed in rooms with > 12 air exchanges/hour and point-of-use HEPA filters that are capable of removing particles > 0.3 μm in diameter" (ie, fungal spores). And again "Correct filtration is critical in HSCT centers with ongoing construction and renovation." However, they did so on the basis of expert opinion only. Why?

First, invasive fungal diseases can be devastating for the patient, his or her family and friends, other patients and their carers, and it is costly in many ways. Second, treatment is still often given too late because of the difficulties in confirming the diagnosis. Third, there is no approved broad-spectrum antifungal prophylaxis. That leaves only one measure that hospitals can take — reducing exposure to the offending spores. In the series of published studies, however, times have changed, even since 2000 when these recommendations were published, not least because of tighter budget control and the climate of evidence-based medicine to help decide between competing priorities. Consequently, a report like that of Eckmanns et al would be seized upon for showing that there is a lack of the evidence, even though Eckmanns et al have very carefully stated that no definite conclusions could be drawn from the data. The gauntlet has been thrown to the ground and awaits a group of intrepid researchers to take up the challenge. In the meantime, the original recommendation of the CDC/IDSA should stand until evidence to the contrary is actually found. ■

Hepatocyte Apoptosis in Hepatitis C/HIV Co-Infection

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP

Synopsis: *Hepatocytes exposed in vitro to Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) envelope proteins and undergo apoptosis as a result of cell surface binding of the proteins. The studies indicate that HCV/HIV envelope proteins induce hepatocyte apoptosis by activating a novel downstream STAT1 signaling pathway.*

Source: Balasubramanian A, et al. Signal Transducer and Activator of Transcription Factor 1 Mediates Apoptosis Induced by Hepatitis C Virus and HIV Envelope Proteins ni Hepatocytes. *J Infect Dis*. 2006;194:670-681.

THIS INTERESTING PAPER FROM GROOPMAN'S LABORATORY at Beth Israel in Boston, reports the results of

some elegant experiments designed to elucidate potential mechanisms, accounting for the innocent bystander hepatocyte apoptosis previously observed as a result of binding of HCV and HIV proteins.[1-3] Activation of STAT1 by HCV-E2 and HIV-gp120 proteins was demonstrated in HepG2 cells by DNA binding using a label-specific probe in gel shift assays. HepG2 cells were also transiently transfected with various luciferase-containing constructs. Chemiluminescence detection showed a 2.6-fold increase in luciferase activity in the HCV-E2/HIV-gp120-costimulated cells in cells transfected with the pGAS-TA-Luc vector, compared with unstimulated transfected cells. No change, however, was detected in the transfected cells stimulated with HCV-E2 or HIV-gp120 alone.

Another set of experiments demonstrated tyrosine and serine phosphorylation of STAT1 induced by HCV-E2/HIV-gp120. Phosphorylation of STAT1 had previously been shown to result in dimerization of this protein and translocation to the nucleus, resulting in transcription of target genes. Additional experiments using both Western blotting and immunoprecipitation assays demonstrated that tyrosine phosphorylation of STAT1 was mediated by Lyn kinase. Another set of experiments demonstrated that p38 mitogen-activated protein (MAP) kinase was also involved in STAT1 tyrosine phosphorylation. A series of elegant experiments using both an inhibitor of PKCdelta and PKCdelta single-stranded inhibitory (si) RNA can mediate STAT1 serine phosphorylation after HCV-E2/HIV-gp120 costimulation. Mechanistic experiments demonstrated that STAT1 contributes to FasL-mediated apoptosis in the presence of HCV/HIV envelope protein costimulation, as well as STAT1 enhancement of mitochondrial apoptotic pathways associated with cytochrome c leakage. Finally, STAT1 mediation of caspase 3 activation in HCV-E2/HIV-gp120-induced apoptosis was demonstrated.

COMMENTARY

While modern antiretroviral therapy has been responsible for a dramatic decrease in the mortality rate of HIV over the last 10 years, increasing evidence points to the relatively greater burden of chronic liver disease due to HCV as a cause of morbidity and mortality in HIV patients. It is also generally universally accepted that the severity and rate of progression of HCV-associated chronic liver disease are greatly increased in HIV infected patients.

One of the things that I have always loved about the subspecialty of infectious diseases is the close relationship between the laboratory and the bedside. The last 140 years have shown steady progress in the understanding of the complex interface between the pathogen and the host. This particular paper caught my attention because, in a series of elegant experiments that tease out the effects of how HCV and HIV envelope proteins contribute to apoptotic hepatocyte death, it demonstrates mechanisms responsible for a clinically important phenomenon. While my personal opinion remains that real progress in treatment of HCV will be made with the development of small molecule inhibitors of viral-specific processes (such HCV protease or helicase), the demonstration of the importance of these STAT1-mediated signaling events suggest another route for development of therapeutic strategies for HCV/HIV coinfection.

It may be of interest to know a little about the senior author of this paper, Dr. Jerome Groopman, who is a Professor of Medicine at Harvard and a hematologist/oncologist by training. Many years ago when I was doing basic research in HIV, I would see Jerry at various meetings and we would occasionally talk about science or life. I was always impressed with his wisdom and kindness, which clearly went to the core of his being. Many years later, I read a review in the *New York Times* of his first book written for lay people, "The Measure of Our Days," published in 1997, which details the spiritual lives of several patients as they reach the end of their physical lives. His 2000 book, "Second Opinions: Stories of Intuition and Choice in the Changing World of Medicine" is excellent as well. These 2 books were later used as the takeoff for the television series, "Gideon's Crossing." Jerry is a wonderful example of that kind of person who is an excellent scientist, doctor, husband, and father, and someone who combines all of that with a deep spiritual awareness. ■

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Update on the CNS Adverse Effects of Sustiva® (Efavirenz)

SPECIAL FEATURE

By Kiron Punwani, Shannon Suedkamp, Diem Nguyen, and Jessica C. Song

Kiron Punwani, Shannon Suedkamp, and Diem Nguyen are PharmD Candidates at the University of the Pacific School of Pharmacy. Jessica C. Song, MA, PharmD, is Pharmacy Residency Coordinator, Santa Clara Valley Medical Center

Kiron Punwani, Shannon Suedkamp, Diem Nguyen, and Jessica C. Song report no financial relationships relevant to this field of study.

Introduction

THE US DEPARTMENT OF HEALTH AND HUMAN Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents recommends efavirenz (EFV) as part of the preferred non-nucleoside reverse transcriptase inhibitor-based regimen for HIV patients.[1] EFV represents a frequently used component of several antiretroviral combination regimens, even though many patients report CNS (central nervous system) side effects.

Studies, to date, have limited data on non-Caucasian patients, despite the fact that according to the DHHS, the AIDS rate for Hispanic adults and adolescents was 25 per 100,000, compared to 7.1 for Whites and 72.1 for Blacks.[2] Hence, there is a compelling need to study this population segment. Of note, post-marketing surveillance of EFV revealed numerous cases of CNS adverse effects associated with elevated plasma concentrations of this drug, especially in the non-Caucasian patient population.[3-6]

This article will present a review of: 1) case reports of EFV-associated CNS effects observed in patients with elevated concentrations of this drug; 2) differences in pharmacokinetic profiles between Caucasian and non-Caucasian populations; and 3) monitoring recommendations for patients receiving this drug.

Published Reports of CNS Toxicity

Previous studies have evaluated CNS side effects associated with EFV plasma levels.[3-6] A study conducted by Marzolini and colleagues showed that EFV plasma concentration levels help predict treatment failure and CNS side effects. Virologic failure occurred in 22% of patients with EFV levels of 1000-4000 ug/L, and CNS toxicity was 3 times more frequent in patients with EFV levels greater than 4000ug/L compared with patients whose levels ranged from 1000 to 4000ug/L. This study also confirmed the presence of marked inter-patient and low intra-patient variability, suggesting that therapeutic drug monitoring may be useful for individualizing treatment.[3]

Various patient populations have been studied, but Hispanic patients were often under-represented. For example, Gutierrez and colleagues demonstrated that a predominantly Caucasian patient population (94.1%) with EFV plasma concentrations greater than 2.74ug/mL were 5.68 times more likely to experience CNS toxicity.[4] Findings from a study performed by Ribaudo and colleagues supported the strong association of race with the clearance of EFV. The clearance increased by 32% in White non-Hispanic subjects, compared with Black and Hispanic subjects; possibly due to differences in metabolism. Of note, patients in this study consisted of 53% Caucasian, 32% Black, and only 15% Hispanic.[5]

A report published by Hasse and colleagues described the case of a 33-year-old, HIV-infected Taiwanese woman who exhibited symptoms of acute psychosis, resulting from her EFV- based antiretroviral (ARV) regimen. About a week after treatment cessation, all psychiatric symptoms disappeared. Since the patient's symptoms were attributed to an interaction between EFV and fluconazole, interventions included a lowering of her fluconazole dose from 400 mg to 200mg once daily and re-initiation of her EFV-based ARV regimen. Her psychiatric symptoms reappeared, and her EFV level was discovered to be 30-fold higher than the upper normal limit. EFZ is metabolized by cytochrome (CYP) 2B6, and the inter-individual differences in CYP2B6 activity may be responsible for the differences in susceptibility to EFV associated CNS side effects.[6]

Differences Between Caucasian and Non-Caucasian

EFV undergoes metabolism by cytochrome p450 (CYP) 2B6 to form inactive hydroxylated metabolites that include 8- and 7-hydroxy efavirenz.[7] Genetic polymorphisms of the CYP2B6 isoenzyme have been shown to increase plasma concentrations of EFV in susceptible individuals exposed to this drug.

Single nucleotide polymorphisms of CYP2B6 arise from the 2B6*6 allele (15631G > T (Q172H); 18053A > G (K262R)), with the highest frequencies seen in African-Americans.[8-9] Less is known about the inci-

Table 1
CYP2B6 Substrates, Inhibitors, Inducers

	SUBSTRATES[7,10-11]	INHIBITORS[12-14]	INDUCERS[15-17]
Efavirenz	X		
Bupropion	X		
Cyclophosphamide	X		
Ifosphamide	X		
Thiotepa		X	
Clopidogrel		X	
Ticlopidine		X	
Levonorgestrel/estradiol		X	
Phenobarbital			X
Phenytoin			X
Rifampin			X

dence of CYP2B6 polymorphisms in the Hispanic population. One study conducted by Ribaudo et al demonstrated that Caucasians exhibited a 32% higher clearance of EFV compared with the clearances observed in African-Americans and Hispanics.[5]

Monitoring Recommendations

Several studies have documented the effects of various drugs on CYP2B6 activity. *Table 1* summarizes the drug-interaction profile of EFV, as shown by the list of CYP2B6 substrates, inhibitors, and inducers.[7,10-17]

In order to anticipate EFV-associated CNS effects, physicians should monitor for drug interactions of this drug with CYP2B6 inhibitors. Furthermore, plasma concentration level monitoring may be warranted in patients with intolerable CNS adverse effects, with levels being drawn 12 hours post-dose.[3-4]

Conclusion

To date, numerous studies have demonstrated that high plasma levels of EFV are associated with CNS side effects, and some have shown inter-patient variability that may be due to race and/or genetic polymorphisms involved in the metabolism of EFV. Although the populations studied have included Hispanic patients, they have represented only a small percentage, and the focus has been primarily on Caucasian populations. In light of the fact that Hispanics account for an estimated 19% of total AIDS diagnoses in the United States,[2] physicians should be particularly alert for signs of EFV-induced toxicity in this under-studied population. ■

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CME Questions

10. Which of the following is correct with regard to darunavir?
a. It is a non-nucleoside reverse transcriptase inhibitor.
b. It is a nucleotide analog reverse transcriptase inhibitor.
c. It must be given together with ritonavir.
d. It is not metabolized by the CYP450 enzymes.

11. Which of the following is correct with regard to the results of treatment trials in patients with *Clostridium difficile*–associated diarrhea?
a. The combination of rifampin with metronidazole was shown to be superior to metronidazole alone.
b. Nitazoxanide was shown to be inferior to metronidazole.
c. All doses of tolevamer were shown to be inferior to vancomycin.
d. Tolevamer is not an antibiotic.

12. Which of the following is correct with regard to efavirenz?
a. Plasma levels are not predictive of therapeutic success or failure.
b. Plasma levels are not predictive of central nervous system side effects.
c. It is metabolized by the 2B6 isoform of CYP450.
d. The coadministration of rifampin does not efavirenz exposure.

Answers: 10. (c); 11. (a); 12. (c)

CME Objectives

The objectives of *Infectious Disease Alert* are:

• To discuss diagnosis and treatment of infectious diseases;

• To present current data regarding use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• To present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• To discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Measles

UPDATES

By Carol A. Kemper, MD, FACP

VZIG — No Longer Available

VariZIG for Prophylaxis after Exposure to Varicella. *Med Lett Drugs Ther*. 2006; 48:69-70.

THE ONLY MANUFACTURER OF VZIG in the United States recently stopped its production. An alternate product, VariZIG, which is manufactured by a Canadian company and has not been approved for use in the United States by the FDA, can be obtained in the United States, but only through expanded access as an investigational new drug. VariZIG is prepared from pooled human plasma, similar to VZIG, and has been treated with filtration and inactivation methods. As such, there remains a small risk of transmission of blood born pathogens.

Varicella immune globulin is indicated for those exposed patients who are at high risk for complications from varicella infection, for whom varicella vaccination is contraindicated. In the United States, these include: non-immune pregnant women; non-immune immunocompromised persons; neonates born to mothers with varicella infection between 5 days before and 2 days after delivery; premature infants > 28 weeks gestation born to non-immune mothers; and premature infants < 28 weeks gestation or who weigh < 1000 grams who are exposed regardless of the mothers immune status.

The expanded access protocol has central IRB approval, but local institutional approval may be needed. In order to receive VariZIG in the United States, contact FFF Enterprise, which is the only authorized distributor (24 hour telephone number (800) 843-7477). The company will review eligibility before shipping the drug within 24 hrs. Signed informed consent is required, and a brief case record form with 4 visits is required. ■

Prosthetic Joint Infection

Marculescu CE, et al. Outcome of Prosthetic Joint Infections Treated with Debridement and Retention of Components. *Clin Infect Dis*. 2006; 42:471-478.

DEBRIDEMENT AND RETENTION OF components is commonly employed for the treatment of prosthetic joint infection (PJI), especially for those who are poor candidates for a second (or third) joint replacement. In this retrospective review, Marculescu and colleagues assessed all patients with a total hip or knee arthroplasty who developed PJI and underwent debridement and retention of components between 1995 and 1999 at the Mayo Clinic in Rochester, Minnesota. A total of 99 PJI occurred in 91 individuals, with a median age of 74. About one-third of the patients were febrile, 13% had evidence of radiographic lucency, and 6% were bacteremic. Patients underwent a median of one surgical debridement (range, 1-4) but just the first was considered for statistical purposes. Purulence was noted in 56% of the cases. The polyethylene parts were exchanged in addition to debridement in nearly half of the cases.

S. aureus and coagulase-negative staphylococci were the most common organisms identified in culture (32% and 23% of the cases, respectively), followed by *Streptococcal* spp (14%), gram negative organisms (6%), enterococci (3%), and anaerobic infection (1%). Eight (8%) of the cases were polymicrobial and 8% were culture negative.

Of the 99 episodes, 93 were treated with parenteral antibiotics for a median of 28 days (range, 1-90 days); 6 episodes were treated with oral antimicrobials, including oral fluconazole in one case. Following this, 89% of the episodes were treated with long-term chronic oral suppressive antimicrobial therapy for a median of 541 days (range, 5-2673 days); in 11 episodes, long term suppressive therapy (LTST) was not administered; 6 of these patients either rapidly failed parenteral therapy or died.

A total of 46 (52%) of 88 episodes treated with LTST ultimately recurred; 9 of whom had stopped their treatment. Only one of 10 persons who stopped their LTST therapy remained disease free. Of those who did not received LTST, treatment failure occurred in 7 of 11 (63%) of episodes. The other 4, 3 of whom were initially culture negative, remained disease free at follow-up.

The overall 2-year disease-free survival rate was 60% (95% confidence interval, 50%-71%). Risk factors for treatment failure included the presence of a sinus tract (hazard ratio 2.84) and duration of symptoms prior to surgery > 8 days (hazard ratio 1.77). The 2-year disease-free survival rate for patients with *S. aureus* infection was 22%, compared with 82% for PJI episodes due to coagulase-negative Staphylococci or *Streptococcal* spp. There was no association between the risk of treatment failure and a history of diabetes, rheumatoid arthritis, prosthesis age, or prosthesis loosing. Debridement and retention of prosthesis in patients with infected THA/TKR may be an attractive option, especially for those patients who are not

good surgical candidates or for those with non-*S. aureus* infection. However, long-term suppressive antibacterial therapy (without an apparent end point) was necessary to prevent relapse most cases. ■

Public Health Cost of Imported Measles

Parker AA, et al. Implications of a 2005 Measles Outbreak in Indiana for Sustained Elimination of Measles in the United States. *N Engl J Med*. 2006;355:447-455. Erratum in: *N Engl J Med*. 2006;355:1184.

PARKER AND COLLEAGUES describe the public health effort required to contain the largest outbreak of measles occurring in the United States in the past 10 years. The outbreak, which occurred in Indiana in 2005, began when a 17-year-old girl who was incubating measles arrived from Romania. The following day she attended a church gathering with ~500 people. Within days, a 6-year-old girl attending the event was hospitalized. The outbreak quickly spread in this highly unvaccinated community — largely because of the presence of unvaccinated children of parents who were concerned about the safety of measles vaccination.

Over the next 6 weeks, 3 waves of measles infection occurred. Sixty-six persons were suspected to have measles; 34 persons were confirmed. Fifty individuals lacked immunity to measles (~10% of the gathering), and evidence of vaccine failures occurred in 2 infected individuals. Three patients required hospitalization, including a hospital phlebotomist who developed pneumonia requiring ventilatory support for 6 days.

Virus isolated from 4 of the patients was identical, and all were genotype D4, which is endemic to Eastern Europe, as well as the Middle East and India.

Parker et al estimate that containment of the outbreak involved 3 different public health departments, 29 public health employees, 3650 person hours, and 4800 telephone calls; an estimated cost of $168,000 (~$5000 per infected patient). A total of 465 doses of MMR and 210 doses of prophylactic immune globulin were administered.

Importation of measles infection remains the single most important source of measles in the United States. Individuals in their 30s and 40s may be more vulnerable than previously suspected, possibly due to waning immunity. No nation currently requires measles vaccination for entry, including the United States. While this report was in press, a second, smaller outbreak occurred in Boston in May, 2006, when a young female computer programmer was recruited from India to work at the John Hancock Tower (where ~2000 people work). A total of 14 cases of measles occurred, including 12 employees in the building and 2 other Boston residents. Health care facilities should be alert to the possibility of measles infection in any immigrant or traveler with a febrile exanthem, and promptly alert public health authorities. ■

HBV with de novo Adefovir Resistance

Schildgen O, et al. Variant of Hepatitis B Virus with Primary Resistance to Adefovir. *N Engl J Med*. 2006,354: 1807-1812; Chang TT, Lai CL. *N Engl J Med*. 2006;355:322-323.

NEWER DATA SUGGEST THAT ~2% of naturally occurring HBV may exhibit de novo resistance to adefovir. The authors describe cases of a variant HBV with primary resistance to Adefovir that remained sensitive both in vivo and in vitro to tenofovir (Viread, Gilead Sciences). The 3 patients, 2 of whom were married, were initially treated, and failed lamivudine as part of a clinical trial involving ~80 persons. All 3 subsequently received adefovir without any virologic response, but later responded to tenofovir.

The 3 strains of HBV proved to have the same unique amino acid substitute in the reverse transcriptase domain (rtI233v). The mutation was independent of lamivudine resistance, and remained stable for up to 220 weeks, even in the absence of selective pressure from adefovir. All 3 strains were typed a genotype D, which has a worldwide distribution and is the most common HBV genotype. A GenBank search found only 3 of 500 previously sequenced strains containing this mutation (2 from southeast Asia, both genotype C, and one from a Gibbon).

The initial significance of this mutation was not clear. Strains containing the mutation exhibited reduced in vitro sensitivity to adefovir by a factor of about 6 to 10, compared with wild type virus. Site-directed mutagenesis, whereby the isoleucine group at position 233 was converted back to wild type virus containing valine, demonstrated adefovir-sensitive virus.

Separately, another clinical trial compared the effectiveness of entacavir and lamivudine in patients with HBV infection. Eight patients receiving entacavir were found to be infected with a rtI233V mutant strain. Seven of the 8 patients developed undetectable viral loads, and 6 of 6 with available histologic data had histologic improvement. Although these patients did not have pre-existing lamivudine resistant, entecavir may be a good therapeutic option for patients with this variant mutation. Although tenofovir is not approved for use in patients with HBV, HIV providers have been using it successfully as part of an antiretroviral regimen for HBV/HIV co-infected persons. ■

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.

The Indictment of Pharma Industry Marketing Practices

A team from UCSF recently reviewed company documents that were entered into the public record as a result of litigation over the promotion of gabapentin (Neurontin) between 1994 and 1998. The result, a rather scathing indictment of the pharmaceutical industry's marketing practices, is published in the August 15 *Annals of Internal Medicine*.

The authors had access to thousands of pages of inside company documents from Pfizer, Parke-Davis, and Warner-Lambert regarding the marketing of gabapentin during a time that the drug was a blockbuster, with sales in the hundreds of millions of dollars.

The primary focus of the litigation was the promotion of off-label indications of gabapentin by Parke-Davis. The paper highlights the company's marketing strategy, which included identifying groups of physicians for targeted marketing. Local champion physicians were identified and trained as "peer-to-peer selling" program leaders. The company also identified physician thought leaders in academic medicine who were given large honoraria, research grants, and educational grants to promote the drug. Resident physicians were also targeted, and large sums of money were given to residency programs. Medical education was one of the cornerstones of the marketing plan.

Physician lectures, teleconferences, and other meetings were set up discuss treatment of epilepsy, but also to discuss off-label use of the drug. Parke-Davis employees frequently surreptitiously listened in on these meetings electronically, in part to gauge the effectiveness of the presentation. Physician moderators were paid well for their participation.

Parke-Davis also developed speaker's bureaus and created academic neurologic lecture series for the neurology community. Department chairs and clinical training program directors were frequently on the speakers lists of these programs. The company also gave unrestricted grants through third-party medical education companies which allowed speakers to legally discuss off label use of gabapentin and to grant CME credits.

A Parke-Davis memo describes these activities as a "growth opportunity" for off-label use of the drug. Physician advisory boards were also well paid to attend meetings where promotional activities were discussed. Research was also directed by the company, and there are indications that studies that gave favorable outcomes were more likely to be published than studies that were not favorable to the drug.

The company also promoted review articles and letters to the editor of journals regarding gabapentin for as much as the $18,000 per article. The authors point out that activities "traditionally considered independent of promotional intent" such as CME and research were corner-

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stones of marketing efforts, and when run through a third party, were legal marketing forums for off-label uses of the drug. The authors call for new strategies to "ensure a clear separation between scientific and commercial activity" (*Ann Int Med*. 2006;145:284-293). This paper is a must read for anyone involved in formulary management, cost effective prescribing processes, or medical education.

TNF Blockers: Should You Be Concerned?

The use of TNF blockers for treatment of rheumatoid arthritis has always been clouded by the potential risk of lymphoma or solid cancers. A new study suggests that the concern may be unfounded.

Researchers from Harvard and University of British Columbia performed a cohort study pooling data from 1152 RA patients who received a biologic DMARD (the TNF blockers etanercept, infliximab, adalimumab, or anakinra) and 7306 patients who received methotrexate. Both groups of patients had elevated risks of cancer compared to the general population, but the overall hazard ratio for hematologic and solid tumors for patients receiving a biologic DMARDs vs methotrexate was 0.98 (1.11 lymphoproliferative cancers 1.37 for hematologic malignancies, and 0.91 for solid tumors).

The authors conclude that biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with methotrexate users (*Arthritis Rheum*. 2006;54:2757-2764).

FDA Actions

The FDA has approved over-the-counter access for Plan B, the so-called morning-after pill. Over-the-counter sales of Plan B have been a contentious issue on Capitol Hill throughout the Bush presidency, and it took a change in leadership in the FDA to bring about the change in position. Plan B will be available for women ages 18 and older without a prescription; however, a prescription is still required for women ages 17 and younger. Plan B is marketed by Duramed, a subsidiary of Barr Pharmaceuticals.

Several SSRI antidepressants have made the switch to generic, including fluoxetine, paroxetine, citalopram, and sertraline. Now the first generic serotonin/norepinephrine reuptake inhibitor has been approved. Venlafaxine (marketed as Effexor) was approved for generic switch in August in 25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg strengths. TEVA pharmaceuticals have exclusivity on the generic for 180 days.

The FDA has approved the use of clopidogrel (Plavix -Bristol-Myers Squibb) in patients with ST segment elevation myocardial infarction (STEMI) who are not going to have coronary artery interventions. The new indication for the drug was based on the findings of 2 studies (COMMIT and CLARITY), which showed improved outcomes with use of the drug in STEMI patients, including those who had initial thrombolytic therapy.

In related news, a somewhat bizarre patent battle over clopidogrel is raging between Bristol-Myers Squibb and Canadian generic maker Apotex. The Canadian company challenged the patent, and introduced generic clopidogrel to the American market on August 8. On August 31, a federal judge in New York issued a restraining order to block distribution of the generic version of the drug; however, she did not require a recall of the generic pills already on the market. Bristol-Myers, which derives 30% of its yearly profit from sales of Plavix, is unsure how much generic product was distributed in 4 weeks; most estimates are approximately 3 months supply. Meanwhile, the patent trial is scheduled to begin in January.

The FDA's Center for Drug Evaluation and Research has issued a warning regarding concomitant use of ibuprofen and aspirin for patients who are taking aspirin for cardioprotection. Functional studies have shown that ibuprofen blocks the effect of aspirin on platelets if the 2 drugs are taken at the same time. Both drugs inhibit cyclooxygenase on platelets. Aspirin's effect is irreversible for the life of the platelet, whereas ibuprofen and other NSAIDs cause reversible inhibition. If ibuprofen is taken before or concomitantly with aspirin, the receptor site is occupied and aspirin is unable to exert its effect. However, if aspirin is taken 30 minutes before ibuprofen or 8 hours after, there is no competitive inhibition. The FDA is recommending that physicians be aware of the timing of ibuprofen and, perhaps, other NSAIDs when used with aspirin, and specifically recommend that aspirin be given 30 minutes prior to ibuprofen or 8 hours later. Recommendations regarding enteric-coated aspirin are unavailable at this time. ■