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INSIDE

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Posaconazole for Azole-Refractory Candidiasis in Patients with HIV Infection

ABSTRACT AND 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 serves as a consultant to Siemens Diagnostics and is on the Speakers Bureaus of Boehringer-Ingelheim and GSK.

Synopsis: *176 HIV-infected patients with either oropharyngeal candidiasis (OPC) or esophageal candidiasis (EC) who had not responded to standard courses of either fluconazole or itraconazole were treated with posaconazole. 132 (75%) of patients achieved a clinical response. The 2 regimens tested were generally well-tolerated with only 8 patients (4%) discontinuing treatment due to a treatment-related adverse event.*

Source: Skiest DJ, et al. Posaconazole for the treatment of azole-refractory oropharyngeal and esophageal candidiasis in subjects with HIV infection. *Clin Infect Dis*. 2007;44:607-614.

THIS PAPER REPORTS THE RESULTS OF AN IMPORTANT MULTINATIONAL trial which evaluated the use of two different regimens of posaconazole in the treatment of OPC or EC which had been refractory to either fluconazole or itraconazole. The 2 regimens studied were oral posaconazole 400 mg BID for 3 days followed by 400 mg once daily for 25 days or posaconazole 400 mg BID for the entire initial 28 days. After 28 days on the induction regimen patients who had clinically responded could receive posaconazole 400 mg BID 3 times/week as suppressive therapy for up to 3 months.

Both dosing regimens were equally effective. Posaconazole was active against both Candida albicans and other Candida

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species. The posaconazole regimens were also effective in patients from whom Candida isolates demonstrated in vitro resistance to either or both fluconazole and itraconazole.

COMMENTARY

Despite the significant reduction in the prevalence of severe and refractory mucosal candidiasis in HIV patients due to the use of HAART, management of OPC and EC refractory to older azoles remains a relatively common clinical problem. While parenteral echinocandins and amphotericin B preparations are extremely useful in acute treatment of esophageal candidiasis, they are a very heavy hammer with which to treat recurrent OPC. As a result we are often left with a number of unsatisfactory measures to try to manage OPC which is refractory to fluconazole or itraconazole. Oral voriconazole is often ineffective due to cross-resistance with the older azoles. Anecdotally some clinicians have found success with pushing the doses of older azoles but I have never been impressed that this works for long and is often complicated by hepatotoxicity and significant drug interactions in the case of itraconazole. Nystatin oral suspension has seldom been effective in my hands nor has the use of "homebrew" oral suspensions of amphotericin B, which I have occasionally tried out of desperation in the past.

Posaconazole is a broad spectrum antifungal triazole with in vitro activity against many molds as well as most fluconazole and itraconazole resistant yeasts. Posaconazole received FDA market clearance in the fall of 2006.

These results are encouraging and show that posaconazole is a useful addition to our therapeutic armamentarium for the treatment of azole-refractory and azole-resistant OPC and EC. However, the trial only followed patients out for a few months. As we know from our experience in the past with treating recurrent mucosal candidiasis with the older azoles in the setting of HIV infection, development of resistance to posaconazole in vivo is likely to occur. Reversal of the underlying HIV-related immunosuppression is ultimately the best way to suppress all opportunistic infections. ■

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Azithromycin for Traveler's Diarrhea in Thailand

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Source: Tribble DR, et al. Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. *Clin Infect Dis.* 2007; 44:338-346.

Synopsis: *A randomized trial found that the optimal therapy for empiric treatment of diarrhea acquired by travelers in Thailand was a single 1 gram dose of azithromycin.*

U.S. MILITARY PERSONNEL IN THAILAND PRESENTing with the acute onset of diarrhea were randomized to treatment with one of 3 regimens: a single 1 g dose of azithromycin, 500 mg of azithromycin daily for 3 days, or 500 mg levofloxacin daily for 3 days. One or more enteric pathogen was identified in 81% of patients of the 156 patients, with Campylobacter accounting for 64% of this group. All the Campylobacter isolates were susceptible to azithromycin (MIC90, 0.094 mcg/ml), while 50% were resistant to levofloxacin. Of the 28 Salmonella isolates, 14% were resistant to azithromycin while none were resistant to azithromycin. There were 18

enteropathogenic *Escherichia coli* isolates; 3.8% and 5.6% were resistant to levofloxacin and azithromycin, respectively. All 11 Plesiomonas isolates were susceptible to both antibiotics.

The cure rate at 72 hours among azithromycin recipients in an intent-to-treat analysis was 94% in the single dose group and 80% in the 3 day treatment group, but only 70% in those given levofloxacin for 3 days ($P = 0.001$). The one day azithromycin treatment was significantly superior to the 3 day regimen ($P = 0.04$). The mean duration of diarrhea after the first dose of antibiotic was 39 hours and 43 hours in the single and multiple dose azithromycin groups and 43 hours in those treated with the fluoroquinolone.

Microbiological eradication was achieved in 96% -100% of azithromycin recipients and only 38% of those given levofloxacin ($P = 0.001$), but there was only a weak correlation between pathogen eradication and clinical response. Although many subjects were receiving doxycycline as malaria prophylaxis, analysis determined that this did not appear to affect the results. Treatment was well tolerated, although nausea after the first treatment dose occurred significantly more frequently in individuals who received a single 1-g dose of azithromycin.

COMMENTARY

The recently published recommendations of the Infectious Disease Society for the management of traveler's diarrhea[1] can be summarized as follows:

• Pre-travel management includes education and advice about prevention, food and liquid hygiene, and provision of self-treatment if diarrhea occurs.

• Self-treatment is multi-component and includes hydration, the use of loperamide for symptom control when necessary (but in the absence of temperature > 38.5° C, and a short course of antibiotics.

• Therapy with a single dose or up to 3 days of therapy with a fluoroquinolone is generally recommended, but in travelers to destinations (Southeast and South Asia) with a high prevalence of fluoroquinolone-resistant Campylobacter infections, "azithromycin may be indicated."

This study confirms the efficacy of azithromycin in the treatment of traveler's diarrhea as well as its superiority to levofloxacin in a location with significant fluoroquinolone resistance among ampylobacter isolates. Unfortunately, such resistance is not confined to Thailand, having been recognized in other parts of Asia and, more recently, in South America and Africa. Azithromycin has also been demonstrated to be effective in the treatment of typhoid fever, including cases caused by multidrug resistant isolates.[2]

References:

1. Hill DR, et al. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006; 43:1499-1539.
2. Parry CM, et al. Randomized controlled comparison of ofloxacin, azithromycin and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. *Antimicrob Agents Chemother*. 2007; 51:819-825.

Advisory Committee on Immunization Practices Issues Guidelines for Gardasil, HPV Vaccine

SPECIAL REPORT

By Stan Deresinski, MD, FACP

Source. CDC. Human Papillomavirus Vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2007; 56:1-24.

THE ADVISORY COMMITTEE ON IMMUNIZATION Practices (ACIP) has finally published its recommendations for the use of Gardasil, the quadrivalent human papillomavirus vaccine that has recently become available. While the essence of these recommendations has been known for some months, their publication is important in that some third party payers resist reimbursement for the vaccine until they appear in print as an official document. The following is a summary of those recommendations.

Who should receive the vaccine?

Routine vaccination is recommended for females at 11-12 years of age, but the 3 dose series may be initiated as early as age 9 years.

What about females older than 12 years of age?

Vaccination is also recommended for females aged 13-26 years who have not been previously vaccinated or who have not completed the full series.

What about females younger that 9 years or older than 26 years of age?

The quadrivalent HPV vaccine is not licensed for use among females aged < 9 years or those aged > 26 years. Studies are ongoing among females aged

> 26 years. No studies are underway in women greater than 26 years of age.

What about females who are already sexually active?

While it is preferable that the vaccine be administered before potential exposure to HPV through sexual contact, females who might have already been exposed to HPV should be vaccinated. Sexually active females who have not been infected with any of the HPV vaccine types receive full benefit from vaccination while vaccination provides less benefit to females if they have already been infected with one or more of the four vaccine HPV types. However, it is not possible for a clinician to assess the extent to which sexually active persons would benefit from vaccination, and the risk for HPV infection might continue as long as persons are sexually active.

Is testing required before vaccine administration?

Pap testing and screening for HPV DNA or HPV antibody are not needed before vaccination at any age.

Should females with an equivocal or abnormal Pap test or who are known to have HPV infected be vaccinated?

Females who have an equivocal or abnormal Pap test could be infected with any of approximately 40 high-risk or low-risk genital HPV types. Such females are unlikely to be infected with all four HPV vaccine types, and they might not be infected with any HPV vaccine type. Vaccination would provide protection against infection with HPV vaccine types not already acquired. With increasing severity of Pap test findings, the likelihood of infection with HPV 16 or 18 increases and the benefit of vaccination would decrease. Women should be advised that results from clinical trials do not indicate the vaccine will have any therapeutic effect on existing HPV infection or cervical lesions.

Females who have a positive HC2 High-Risk test conducted in conjunction with a Pap test could have infection with any of 13 high-risk types. This assay does not identify specific HPV types, and testing for specific HPV types is not conducted routinely in clinical practice. Women with a positive HC2 High-Risk test might not have been infected with any of the four HPV vaccine types. Vaccination would provide protection against infection with HPV vaccine types not already acquired. However, women should be advised that results from clinical trials do not indicate the vaccine will have any therapeutic effect on existing HPV infection or cervical lesions.

Does the presence or history of genital warts obviate the need for vaccination?

A history of genital warts or clinically evident genital warts indicates infection with HPV, most often type 6 or 11. However, these females might not have infection with both HPV 6 and 11 or infection with HPV 16 or 18. Vaccination would provide protection against infection with HPV vaccine types not already acquired. However, females should be advised that results from clinical trials do not indicate the vaccine will have any therapeutic effect on existing HPV infection or genital warts.

Can a woman who is lactating receive the vaccine?

Yes.

What about vaccination during pregnancy?

Quadrivalent HPV vaccine is not recommended for use in pregnancy. The vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events in the developing fetus. However, data on vaccination during pregnancy are limited. Until additional information is available, initiation of the vaccine series should be delayed until after completion of the pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed. A vaccine in pregnancy registry has been established; patients and healthcare providers should report any exposure to quadrivalent HPV vaccine during pregnancy (telephone: (800) 986-8999)).

Can immunocompromised patients receive the vaccine?

Because quadrivalent HPV vaccine is a noninfectious vaccine, it can be administered to females who are immunosuppressed as a result of disease or medications. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent.

Can the vaccine be administered to someone suffering from an acute illness?

Quadrivalent HPV vaccine can be administered to persons with minor acute illnesses (eg, diarrhea or mild upper respiratory tract infections with or without fever). Vaccination of persons with moderate or severe acute illnesses should be deferred until after the patient improves.

What about allergies?

Quadrivalent HPV vaccine is contraindicated for persons with a history of immediate hypersensitivity to yeast or to any vaccine component. Data from passive surveillance in Vaccine Adverse Event Reporting

System (VAERS) indicates that recombinant yeast derived vaccines pose a minimal risk for anaphylaxic reactions in persons with a history of allergic reactions to Saccharomyces cerevisiae (baker's yeast).

What is the dose, route of administration and schedule for the vaccine?

The dose of the quadrivalent vaccine is 0.5 mL (shake well before administration) given intramuscularly, preferably in the deltoid muscle. The minimum recommended interval between the first and second doses is 4 weeks. The second and third doses should be administered 2 and 6 months after the first dose. The minimum interval between these two doses should at 12 weeks. The third dose, if delayed beyond the recommended time, should be administered as soon as possible.

Can it be administered together with other vaccines?

The quadrivalent HPV vaccine is not a live vaccine and has no components that adversely impact safety or efficacy of other vaccinations. Quadrivalent HPV vaccine can be administered at the same visit as other age appropriate vaccines, such as the Tdap and quadrivalent meningococcal conjugate (MCV4) vaccines. Administering all indicated vaccines together at a single visit increases the likelihood that adolescents and young adults will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site.

If someone has been vaccinated, do they need to continue cervical cancer screening?

Cervical cancer screening recommendations have not changed for females who receive HPV vaccine. HPV types in the vaccine are responsible for approximately 70% of cervical cancers; females who are vaccinated could subsequently be infected with a carcinogenic HPV type for which the quadrivalent vaccine does not provide protection. Furthermore, those who were sexually active before vaccination could have been infected with a vaccine type HPV before vaccination. Health-care providers administering quadrivalent HPV vaccine should educate women about the importance of cervical cancer screening.

Should males be vaccinated?

Quadrivalent HPV vaccine is not licensed for use among males. Although data on immunogenicity and safety are available for males aged 9-15 years, no data exist regarding efficacy in males of any age, although efficacy studies are in progress.

Patients occasionally experience syncope after receiving injections, including for vaccines. Is this an issue with the quadrivalent HPV vaccine?

Syncope (ie, vasovagal or vasodepressor reaction) can occur after vaccination, most commonly among adolescents and young adults. Among reports to VAERS for any vaccine that were coded as syncope during 1990-2004, a total of 35% of these episodes were reported among persons aged 10-18 years. Through January 2007, the second most common report to VAERS following receipt of HPV vaccine was syncope. Vaccine providers should consider observing patients for 15 minutes after they receive HPV vaccine.

If a patient suffers an adverse event after vaccine receipt, how do I report it?

As with any newly licensed vaccine, surveillance for rare adverse events associated with administration of quadrivalent HPV vaccine is important for assessing its safety in widespread use. All clinically significant adverse events should be reported to VAERS at http://vaers.hhs.gov, even if causal relation to vaccination is not certain. VAERS reporting forms and information are available electronically at www.vaers.hhs.gov or by telephone ((800) 822-7967). Web-based reporting is available and providers are encouraged to report electronically at https://secure.vaers.org/VaersDataEntryintro.htm to promote better timeliness and quality of safety data.

Safety surveillance for adolescent quadrivalent HPV vaccine, Tdap, MCV4, and other vaccines is being conducted on an ongoing basis in cooperation with FDA. A vaccine in pregnancy registry has been established by Merck and Co., Inc.; patients and health-care providers should report any exposure to quadrivalent HPV vaccine during pregnancy (telephone: ((800) 986-8999).

What is the duration of protection provided by the vaccine?

As with any new vaccine, the duration of protection is not yet known. Long-term data on duration of antibody response and clinical protection will be obtained through studies conducted in the Nordic countries through the Nordic cancer registries and through other studies in the United States. Follow up of vaccine trial participants aged 9-15 years will continue for up to 10 years after dose 3. This will include evaluation of antibody titers and, in participants who reach their 16th birthday, evaluation of vaccine effectiveness.

Won't the widespread use of this vaccine simply result in a change in HPV types causing infection?

The prevalence and incidence of HPV types in the vaccine are expected to decrease as a result of vaccination. Studies are planned to monitor HPV types in

various populations and specimens.

How will the long term safety of the vaccine be monitored?

Postlicensure studies to evaluate general safety and pregnancy outcomes will be conducted by the manufacturer and independently by CDC. Monitoring will be accomplished through VAERS and CDC's Vaccine Safety Datalink, which will include surveillance of cohorts of recently vaccinated females and evaluation of outcomes of pregnancy among those pregnant at the time of vaccination. The manufacturer will be monitoring long-term safety as part of the Nordic Cancer Registry Program. ■

RotaTeq Safety

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Source: CDC. Postmarketing Monitoring of Intussusception After RotaTeq™ Vaccination — United States, February 1, 2006 - February 15, 2007. *MMWR.* 2007; 56(10):218-222.

Synopsis: *Passive monitoring has failed to find evidence of an excessive risk of intussusception in infant recipients of RotaTeq.*

ROTASHIELD, A VACCINE PROTECTIVE AGAINST rotavirus infection was withdrawn from the U.S. market because of an apparent excess risk of intussusception. The recent introduction of a new vaccine, RotaTeq, has inevitably led to concerns about an increased incidence of this complication in children receiving this vaccine, as well. Postmarketing surveillance of possible adverse effects of RotaTeq by the Vaccine Adverse Event Reporting System (VAERS) during the first year of its use, however, suggests an absence of increased risk of intussusception.

During February 1, 2006 - February 15, 2007, VAERS received 567 reports of adverse events after RotaTeq vaccination, including 35 reports of confirmed intussusception. One-half occurred within the first 21 days after vaccination with almost one-third occurring within the first 7 days. Fifty-nine percent of affected infants required surgery. When compared to background rates of intussusception in infants, however, the incidence in vaccine recipients was not excessive.

RotaTeq vaccine continues to be recommended for administration to all infants at ages 2, 4, and 6 months. Healthcare providers are reminded that the first dose should be administered to infants only between ages 6 and 12 weeks, and the full series should be completed before age 32 weeks. Monitoring by CDC and FDA will be continued. All persons are encouraged to report cases of intussusception or any adverse events after RotaTeq or any other vaccination to VAERS. Reports may be submitted securely online at www.vaers.hhs.gov or by fax at (877) 721-0366. Reporting forms and additional information are available by telephone at (800) 822-7967. ■

Metabolic Syndrome in HIV-Infected Patients

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 serves as a consultant to Siemens Diagnostics and is on the Speakers Bureaus of Boehringer-Ingelheim and GSK.

Source: Mondy K, et al. Metabolic syndrome in HIV-infected patients from an urban, midwestern U.S. outpatient population. *Clin Infect Dis*. 2007;44:726-734

Synopsis: *471 HIV-infected outpatients were assessed for the presence of metabolic syndrome using standard clinical and laboratory parameters. Compared to HIV-negative subjects selected from the National Health and Nutrition Examination Survey (NHANES) cohort the prevalence of metabolic syndrome was similar.*

THIS IMPORTANT STUDY COMPARED AN OUTPAtient cohort of 471 HIV-infected outpatients living in the Midwest to data files from the NHANES cohort of HIV-negative subjects matched by age, sex, race, and tobacco use. Using standard criteria including waist circumference, blood pressure (or

use of antihypertensive agents), fasting blood glucose and lipid levels (or use of lipid-lowering agents), the prevalence of metabolic syndrome was 25.5% in HIV infected patients and 26.5% in the NHANES cohort.

Looking in greater detail at the cohorts studied, the major risk factors for metabolic syndrome reaching statistical significance, were age, white ethnicity, duration of HIV infection, family history of diabetes and coronary artery disease, elevated BMI and waist circumference. Interestingly the use of highly active antiretroviral therapy (including ritonavir-boosted PIs) did not increase the likelihood of metabolic syndrome.

COMMENTARY

Since the mid-1990s the use of highly active antiretroviral therapy (HAART) has resulted in a dramatic reduction in mortality due to HIV. However, shortly after the introduction of HIV protease inhibitors (PIs), the association between particular PI-based HAART and metabolic complications has been appreciated. Following institution of HAART many patients experience elevations of triglycerides and LDL cholesterol, hyperglycemia (or subclinical insulin resistance), and visceral fat accumulation. These characteristic components of the metabolic syndrome are risk factors for cardiovascular disease.

While this cohort study does not give HAART a clean bill of health, the results are intriguing and suggest that traditional risk factors for metabolic syndrome are of greater importance than HAART in HIV-infected patients. Anecdotally, over the last 12 years I have often noted the phenomenon of some patients who have fairly advanced disease and experience an excellent virologic and immunologic response to HAART develop significant weight gain probably related to improved appetite and overall improved sense of well-being. This occurs on both PI and nnRTI-based HAART. Subconsciously I think many clinicians blame the resultant dyslipidemias or glucose intolerance on the HAART regimen if it contains a PI and on the weight gain if the same abnormalities appear on an nnRTI-containing HAART regimen. The reality, it seems, is that probably the biggest factors for development of metabolic syndrome in HIV-infected patients are the same ones at play in HIV-negative patients.

For those of us who began taking care of HIV patients in the early 1980s and seeing so many of our patients dying of AIDS, having to worry about risk factors for cardiovascular disease in our patients, as we do now, is indeed a blessing. ■

Flu Then Flu Now: New Estimates on Pandemic Influenza Deaths

ABSTRACT & COMMENTARY

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston.

Dr. John does research for Merck, is a consultant for Cubist, Roche, and bioMerieux, and is on the speaker's bureau for Pharmacia, GSK, Merck, Bayer, and Wyeth.

Sources: Murray CJ, et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. *Lancet*. 2006;368:2211-2218.

Webster RG, Govorkova EA. H5N1-influenza — continuing evolution and spread. *N Engl J Med.* 2006;355:2174-2177.

Bresson JL, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase I randomized trial. *Lancet.* 2006;267:1657-1664.

It has become in vogue to plan for influenza pandemics. What is not clear is what would be excess mortality in such a pandemic. Several studies have estimated mortality based on guesses of excessive influenza-related mortality. A new study from Harvard Initiative for Global Health made estimates of all excess mortality, assuming a pandemic with a highly virulent strain of influenza for countries with mortality like that of 1918-1920, for countries which had mortality data before and after the pandemic of 1918-1920.

The study was able to gather data from 28 countries that had recorded excess mortality during the years 1915-1923. The lowest excess mortality was in Colorado (1.0%) and the highest was in 2 states in India, Central Berar (7.8%) and United Provinces (7.1%). Wisconsin had an excess rate of only 0.25% so the increased mortality in Central India was 31 times that of Wisconsin.

Mortality was highest in young adults 15-35 years

of age. Some countries had no excess mortality in persons > 60 years of age. Based on populations in 2004, India would have a median of over 12 million deaths, China about 9 million, Ethiopia 2.7 million, Nigeria 2.3 million, Brazil about 700,000, and the United States about 300,000. The median number of deaths worldwide would be about 62 million, based on the regression model used. When calculations were made for a pandemic occurring in one year, the increase in global mortality would increase by 114% with the highest mortality in the 15-29 year olds.

COMMENTARY

It is true that this study used a type of worst scenario: a pandemic with a virus as virulent that caused the 1918-20 pandemic. Since nearly all individuals living were thought to be exposed by 1920, the authors also argue that modern travel and rapid human mixing would likely not alter the estimates. They also concede that with modern medical care, particularly with intensive care, mortality would likely be lower. Use of antivirals may block some transmission and save additional lives. Vaccination with as long a preparation period of 4-6 months still could alter the epidemic. Finally, deaths in 1918-1920 were commonly due to bacterial pneumonia, so much so that Haemophilus influenzae took its name from its common appearance in the post-mortem lungs of pandemic influenza victims.

What should clinicians as well as public health officials do with these data? First, these high rates of death in no way relate to the probability of such a pandemic occurring. It is somewhat reassuring from my purview that the only "dramatic change in human health" occurred with the 1918-1920 pandemic. Nevertheless, lesser pandemics are probably realizing the penchant for change in the influenza virus. Currently an avian H5N1 virus is making a worldwide reach. It is also possible that while the world watches the global spread of H5N1 from Central China to Japan and Europe, waiting in the wings may be other novel influenza viruses that are much more capable of causing human to human transmission. To avoid catastrophic consequences, these studies suggest a focus on less developed countries where mortality would be highest. Recent H5N1 vaccine trials showed, however, efficacy and short term safety. So there is every reason to hope that modern vaccine development and implementation will buffer the effect of rapid pandemic spread that was so lethal early in the 20th century. ■

Varicella Vaccine, Breakthrough Varicella, and Duration of Immunity

ABSTRACT & COMMENTARY

By Hal Jenson, MD

Chief Academic Officer, Baystate Health Professor of Pediatrics and Dean of the Western Campus of Tufts University School of Medicine

Dr. Jenson is on the speaker's bureau for Merck.

***Synopsis**: Surveillance data from 1995-2004 showed that the risk of breakthrough varicella after a single childhood vaccination dose increased significantly with the time since vaccination. A second dose of varicella vaccine, recommended for all children since June 2006, is expected to improve protection from waning vaccine-induced immunity.*

Source: Chaves SS, et al. Loss of vaccine-induced immunity to varicella over time. *N Engl J Med*. 2007;356:1121-1129.

From community-based active surveillance data in Antelope Valley, California, (northeast of Los Angeles) from 1995-2004, 9.5% (1,080 subjects) of all 11,356 subjects with varicella had onset of rash > 42 days after varicella vaccination, which defines breakthrough varicella. The diagnosis was confirmed by physician evaluation or laboratory test in 770 subjects (71.3%). Children 8-12 yrs of age who were vaccinated > 5 yr previously were significantly more likely to have breakthrough varicella than those vaccinated < 5 yr previously (risk ratio, 2.6; 95% CI, 1.2 to 5.8). The annual rate of breakthrough varicella increased from 1.6 cases per 1000 person-years (95% CI, 1.2 to 2.0) within one year after vaccination to 9.0 cases per 1000 person-years (95% CI, 6.9-11.7) at 5 years and 58.2 cases per 1000 person-years (95% CI, 36.0 to 94.0) at 9 years. The age of disease at onset was the only factor associated with disease severity.

COMMENTARY

These data demonstrate that the immunity induced by a single varicella vaccination during childhood wanes over time and is accompanied by increased incidence of breakthrough varicella that correlates with the time since vaccination. Waning immunity to varicella vaccination is a potentially serious concern because the postponement of varicella from childhood to adolescence and especially adulthood is accompanied by a

much higher risk of severe complications.

Varicella vaccination with the live attenuated live virus vaccine containing the Oka strain was implemented in 1995 with a single dose for all children from 12 months of age to their 13th birthday, and 2 doses for persons >13 yrs of age. A single dose of vaccine in young children results in serologic evidence of immunity in 80%-85% of vaccinees. Clinical data suggest that a second dose of varicella vaccination for children may overcome primary vaccine failure, and also increases the proportion of children with protective antibody titers and enhances cellular immune responses. In June 2006 the Advisory Committee on Immunization Practices recommended that all children between 4-6 yrs of age receive a second dose of varicella vaccine, and also that all children, adolescents, and adults who have previously received only one dose of varicella vaccine receive a second dose. There is no long-term data on the duration of immunity from 2 doses of varicella vaccine in childhood. ■

Pneumococcal Vaccine and Antimicrobial Resistance in Children

ABSTRACT & COMMENTARY

By Hal Jenson, MD

Chief Academic Officer, Baystate Health Professor of Pediatrics and Dean of the Western Campus of Tufts University School of Medicine

Dr. Jenson is on the speaker's bureau for Merck.

Synopsis: *Use of the 7-valent pneumococcal vaccine has resulted in substantial reductions in the prevalence of pneumococcal isolates contained in the vaccine. Antimicrobial resistance among nonvaccine strains in the respiratory tract is increasing.*

Source: Farrell DJ, et al. Increased antimicrobial resistance among nonvaccine serotypes of Streptococcus pneumoniae in the pediatric population after the introduction of 7-valent pneumococcal vaccine in the United States. *Pediatr Infect Dis J.* 2007;26:123-128.

STREPTOCOCCUS PNEUMONIAE ISOLATES WERE collected from children (<14 yrs of age) with community-acquired respiratory tract infections (acute otitis media, community-acquired pneumonia, acute maxillary sinusitis, or acute rhinosinusitis) from 2000-2004 in 112 centers in 38 states. Cultures included blood, sputum, bronchoalveolar lavage fluid, middle ear fluid, sinus aspirates, and nasopharyngeal swabs or aspirates. Serotyping was performed by the Neufeld Quellung reaction and antimicrobial susceptibilities were determined in a central laboratory according to Clinical Laboratory Standards Institute standards.

The proportion of isolates covered by the PCV7 vaccine decreased from 65.5% in 2000-01 to 27.0% in 2003-04 when the most common serotypes were nonvaccine serotypes 19A (19%), 6A (7.8%), 3 (7.6%), 15 (6.3%), and 35B (5.8%), and vaccine serotype 19F (12.7%). Nonvaccine serotype 19A expressing the erm(B) + mef(A) macrolide resistance genotype increased from 7.8% to 45.5%. Antimicrobial resistance among blood isolates remained constant but increased among respiratory tract isolates for penicillin (resistant: 12.7% to 16.1% [$P = 0.0857$]; intermediate susceptibility: 20.1% to 31.5% [$P < 0.0001$]), erythromycin (21.2% to 31.6% [$P < 0.0001$]), amoxicillin-clavulanate (1.4% to 5.8% [$P < 0.0001$]), and multidrug resistance to >2 antimicrobial classes (24.6% to 31.6% [$P = 0.0034$]). A nonsignificant increase was seen for trimethoprim-sulfamethoxazole (25.1% to 28.4% [$P = 0.17$]) and only 1 isolate, in 2003-04, was resistant to telithromycin.

COMMENTARY

These studies do not measure disease burden but document that PCV7 has had a dramatic impact on pneumococcal serotype prevalence among children in the 4 years since its introduction. There have been reductions of vaccine serotypes and emergence of nonvaccine serotypes as the predominant pneumococcal serotypes. This has occurred in both young children < 2 yr of age and among older children 3-14 yr of age. There is some geographic variation among different states reflecting different rates of PCV7 immunization.

Initial surveillance data after the introduction of PCV7 suggested that pneumococcal penicillin and erythromycin resistance declined in isolates from children. Disappointingly, these data now document that resistance to penicillin, macrolides, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, and multidrug resistance all increased in pneumococcal respiratory tract isolates from 2000 to 2004. There was a 3-fold increase from 2000 to 2004 in the prevalence of erm(B) and mef(A) isolates, primarily nonvaccine serotype 19A and vaccine serotype 19F, most of

which are resistant to most antimicrobial classes. (PCV7 has lower efficacy against serotype 19F compared to other vaccine serotypes.)

The changes in pneumococcal serotype distribution resulting from use of PCV7 and the changes in antimicrobial resistance from indiscriminate or inappropriate antimicrobial use are each contributing to a dynamic picture of pneumococcal epidemiology. ■

CME Questions

28. Which of the following is correct with regard to treatment of traveler's diarrhea in Thailand?

A. Three days of azithromycin treatment is significantly superior to single dose treatment with this antibiotic.
B. Levofloxacin is superior to azithromycin.
C. Fluoroquinolone resistance is common among Campylobacter isolates.
D. Azithromycin is ineffective because of its lack of activity against all Gram negative bacillary pathogens.

29. Which is correct regarding the quadrivalent HPV vaccine?

A. It should be routinely administered to females at age 11 - 12 years and has received FDA approval for administration to females ages 9 - 26 years of age.
B. It is contraindicated in a woman with a history of genital warts.
C. It is contraindicated in a woman with a history of an equivocal Pap smear.
D. It obviates the need for cervical cancer screening.

30. What are the current estimates of deaths worldwide that would occur if a 1918-20-like influenza virus caused a modern pandemic?

A. Over 20 million
B. Over 30 million
C. Over 40 million
D. Over 60 million

Answers: 28.(c) 29.(a) 30.(d)

CME Objectives

The objectives of *Infectious Disease Alert* are:

• To discuss the 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:

Vancomycin-induced Thrombocytopenia.

UPDATES

By Carol A. Kemper, MD, FACP

HIV Epidemic in India: Personal Experience From Silicon Valley

Source: R. Steinbrook. HIV in India — A complex epidemic. *N Engl J Med*. 2007;356 (11):1089-1093.

THE SAN FRANCISCO BAY AREA IS now home to one of the largest Asian Indian populations in the United States, especially in Silicon Valley, where it is estimated that 40% of the computer programmers are Asian Indian. As a result, I see more endemic disease (eg, typhoid, salmonella sepsis, malaria and tuberculosis) in a community-based private practice than I ever did at the county hospital. There has been, however, one unique addition to my practice over the past 2 years: 6 Asian Indian patients with HIV, who represent ~5% of my total HIV/AIDS practice. Two are female and 4 are male. One young woman, aged 24 years, has a hidden history of abuse. The other woman is in her early 40s and was a practicing surgeon in India before moving to the United States, where she is a housewife. She presented with a CD4 count of 90 cells/mm^3 but was virtually asymptomatic. The 4 men are bisexual or have had sex with men, though were reluctant to disclose this information. Homosexuality is illegal in India and punishable by the same Penal Code as sex offenders, pedophiles, and people who have sex with animals.

With the exception of the housewife, all work in high tech and were unaware of their HIV status. Infections in all 5 were detected when HIV tested for immigration purposes. While it is possible that the men may have acquired their HIV in the United States, the timing and CD4 cell count results suggest earlier infection.

It is interesting that this experience parallels the emerging epidemic in India, as outlined by Dr. Steinbrook. It is estimated that somewhere between 3.4 and 9.4 million persons in India are infected with HIV, although less than 10% are aware of their status. The estimated prevalence of infection among persons aged 15 to 49 years old is 0.5 to 1.5%. However, prevalence data for much of India is lacking. Of India's 35 states, 6 are considered high prevalence based on observations of HIV seropositive rates > 1% in woman getting prenatal testing and rates > 5% at STD clinics. But many states don't offer prenatal screening, and treatment during pregnancy or peripartum is limited.

HIV prevalence studies in Indian sex workers typically find rates of 10% to 20%, with an estimated number of 2 million female sex workers and 235,000 male sex workers. In addition, India has an estimated 2.35 million men who have sex with men — although many would not identify themselves as such. According to Dr. Steinbrook, sex between men is often considered "mischief."

An important part of the emerging epidemic is the 5 million truckers in India. Similar to the experience in Africa, sex work along the main truck routes is common, bringing the epidemic home to housewives in rural areas. In Chennai (formerly Madras) in southern India, one fourth of HIV+ clients at one treatment center were housewives. Spousal violence against women astoundingly ranges from 16% to 44% , depending on the city. It is no wonder that the Joint United Nations HIV Program in India found "it is not possible to control the overall HIV epidemic if it is out of control in India."

Physicians in the United States should be aware that Asian Indians without readily identifiable risk factors may have HIV. Public health experts advocate stepping up HIV screening in all persons with tuberculosis. Just because someone from India is at increased risk for reactivation TB doesn't mean they don't have HIV. Similar logic should apply to any Asian Indian with salmonella bacteremia, pneumonia, or hospitalization for infection. ■

HIV+ Patients Still Need PCP Prophylaxis

Source: Teshale EH, et al. Reasons for lack of appropriate receipt of primary Pneumocystis jiroveci pneumonia prophylaxis among HIV-infected persons receiving treatment in the United States: 1994-2003, *Clin Infec Dis.* 2007; 44:879-883.

PROPHYLAXIS AGAINST PCP remains the single most cost-effective intervention in HIV+ patients at risk. But treatment has, in some ways, become a moving target in some patients, as their CD4 count rises and falls with newer HIV therapies, medication side effects, and variable compliance. Despite the increased use of highly active antiretroviral therapy, this Atlanta-based clinic reported an unusually high number of PCP cases. During a 4-year period from 1999-2003, 483 cases of PCP were diagnosed during 7315 person years. The incidence in persons receiving both HAART and PCP prophylaxis was low (5.2 episodes per 100 person years). However, the rates of PCP in persons who had an initially favorable CD4 response but later dropped their CD4 below 200 cells/mm^3, those that stopped prophylaxis while their CD4 count was < 200 cells/mm^3, or those that never started below 200 cells/mm^3 were 6.3, 11.3 and 19.2 episodes per person per year,

respectively. Rates for persons with CD4 < 100 were greater.

Women, Latinos, injection drug users, those new to treatment, and those with fewer clinic visits were significantly less likely to receive PCP prophylaxis. Physicians need to be aware of the potential "gap" in PCP prophylaxis for these at-risk subjects. Additional research is needed to determine if there is benefit in maintaining or starting at-risk subjects on PCP prophylaxis at higher CD4 counts, eg, 250 cells/mm^3, recognizing the benefits may outweigh the risks. In addition to decreasing the risk of PCP, prophylaxis with trimethoprim-sulfame-thoxazole has been found to decrease the risk of bronchitis and sinus infection, and recent data found that HIV+ patients maintained on trimethoprim-sulfamethoxazole were at lower risk for infection with MRSA. ■

Increase in Neurocysticercosis in the United States

Source: Sorvillo FJ, et al. Deaths from Cysticercosis, United States. *Emerging Infect Dis.* February 2007; 13(2): www.cdc.gov/eid.

An increasing number of cases of neurocysticercosis are occurring in the Western United States bordering Mexico, and in cities with large immigrant populations, such as New York and Philadelphia. Vouching from personal experience working in a large county hospital in Santa Clara County, California, our state gets more than its fair share of cases. California reported 44 cases of neurocysticercosis in 2005 and 45 cases during the first 10 months of 2006. And those are just the reported cases. Nearly 60% of all U.S. deaths from cysticercosis between 1999-2002 occurred in California residents. The mean age at death was 40.5 years. Only 33 (15%) were U.S.-born, and the rest were foreign born, two-thirds from Mexico. Similarly, the Los Angeles County Public Health Department reported that ~12% of county-based cysticercosis cases had no history of travel and had no significant risk factors for infection.

When doing ward rounds, 3 misconceptions are commonly voiced:

(1) Lack of a recent travel history excludes the diagnosis;

(2) Persons born in the U.S. without a travel history are not at risk for cysticercosis;

(3) Cysticercosis comes from eating "bad pork."

Eating infected pork meat for example, in Mexico, results in the intestinal tapeworm phase of infection with Taenia solium. These persons excrete tapeworm eggs in the stool. Should these individuals migrate across the U.S. border, they can be a source of infection for U.S. residents. Individuals may be exposed by eating fruits or vegetables contaminated in the field (by feces in the soil or by unwashed hands) or from food handlers, restaurant workers, personal cooks or visitors with inadequately washed hands. These ingested eggs pass through the system, migrate through muscle or organs (eg, brain or spinal cord), where they encyst, hoping to be eaten some day, so they can grow up to be a tapeworm. It may take 2-3 years for a person with neurocysticercosis to present with symptoms, typically as the cyst begins degenerating, causing a vigorous immunological response with brain edema and seizures. At that point, treatment of dead or dying cysts may not be helpful. Some patients may simply present years later with seizures from focal scarring from dead cysts. Patients may be left with residual neurologic impairment or chronic seizures. In Hispanics, it is reported that neurocysticercosis results in 13% of all emergency room visits for seizures.

Physicians should keep in mind that, while cystercosis remains an increasingly common problem for Latino immigrants, U.S. born persons without identifiable risk factors may also be affected. ■

Can Influenza Protect You Against Avian Flu?

Source: Sandbulte MR, et al. Cross-reactive neuraminidase antibodies afford partial protection against H5N1 in mice and are present in unexposed humans? *PLoS Med*. 2007Feb 13;4(2):e59.

Hoping to find evidence of cross-protection from infection or immunization with Influenza A and avian flu, these authors immunized a series of mice with DNA vaccine containing human H1N1 viruses. In addition, naïve mice were passively immunized using sera from vaccinated mice. Immunization resulted in a vigorous IgG antibody response with good protection against human Influenza A virus (A/Puerto Rico/8/ 34 with huN1) on challenge.

Partial cross-reactivity was observed when immunized mice were challenged with a lethal dose of either H5N1 virus (A/Vietnam/ 1203/ 2004) or a recombinant avian N1 strain. Passive antibody protection was also protective when non-immunized naïve mice were given a lethal challenge of avian viruses. These data suggest that individuals vaccinated with H1N1 virus, or previously infected with circulating H1N1 virus may have partial cross-protection against avian influenza virus. Seasonal N1-containing Influenza virus circulating within the community may result in anywhere from 10% to 40% of cases, resulting in more durable immunity than that resulting from vaccination. Thus, whether individuals may have partial protection against avian flu without knowing it remains to be determined but seems possible. ■

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.

Which Inhaler Combination is Best for COPD Treatment?

Two recent large studies have looked at the effects of various inhaler combinations on outcomes in patients with COPD. In the first, published in the February 22 issue of the *New England Journal of Medicine*, researchers from the United Kingdom looked at over 6,000 patients with COPD in a randomized, double-blind trial comparing salmeterol plus fluticasone inhaler twice daily (in a single inhaler) vs salmeterol alone, fluticasone alone, or placebo for 3 years. The primary outcome was death from any cause, the frequency of exacerbations, health status, and spirometry values. The all-cause mortality was 12.6% in the combination therapy group, 13.5% in the salmeterol group, 16.0% in the fluticasone group and 15.2% in the placebo group. The hazard ratio for death in the combination therapy group was 0.825 vs placebo ($P = 0.052$), a level that did not reach statistical significance, but was associated with a 17.5% relative reduction in mortality. The mortality rate for salmeterol alone or fluticasone alone did not differ from placebo. Combination therapy was associated with a statistically significant lower rate of exacerbations ($P < 0.001$). The probability of having pneumonia was higher among patients receiving fluticasone alone or medications containing fluticasone (*N Engl J Med*. 2007;356:775-789). An accompanying editorial suggests that the findings show that monotherapy with fluticasone should not be recommended, monotherapy with a bronchodilator may be an option, and that combination therapy "offers statistically significant advantages for health status, frequency of exacerbations, use of oral steroids... and protection against a decline in lung function" (*N Engl J Med*. 2007;356:851-854).

In the second study, 449 patients with moderate or severe COPD were treated with the anticholinergic inhaler tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone/salmeterol. The primary endpoint was COPD exacerbation that required treatment with systemic steroids or antibiotics. After one year there was no difference in the rate of exacerbation between tiotropium alone (62.8%), tiotropium plus salmeterol (64.8%), or tiotropium plus fluticasone/salmeterol (60.0%). Tiotropium plus fluticasone/salmeterol improved lung function ($P = 0.049$), disease-specific quality of life ($P = 0.01$), and reduced the number of hospitalizations for COPD exacerbation and all-cause hospitalization compared with tiotropium plus placebo. The authors conclude that adding fluticasone/salmeterol to treatment with tiotropium did not influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates (early release *Annals of Internal Medicine* 2/20/2007, print date 4/17/2007). So, what is the upshot of these papers? Combination inhalation therapy in patients with COPD works best, bronchodilator plus steroid inhalation therapy should continue to be the recommended regimen perhaps along with an anticholinergic inhaler.

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.

First Antihypertensive Drug Approved in Last 10 Years: Aliskiren

The FDA has approved the first of new class of antihypertensive drugs, and the first new antihypertensive medication to be approved in more than 10 years. Aliskiren is an oral renin inhibitor, inhibiting the renin-angiotensin system earlier in the cascade than angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The drug is a once-a-day oral agent that is approved for use as monotherapy or in combination with other antihypertensives.

Aliskiren's effect is additive with hydrochlorothiazide, and seems to be well-tolerated with other cardiovascular agents. It will be available in 150 and 300 mg doses. The FDA approval was based on 6 placebo-controlled trials in more than 2,000 patients in which the blood- pressure-lowering effect was maintained for up to one year. The drug seems be effective across all age ranges, but is slightly less effective in African-American patients as compared to Caucasians and Asians, as is the case with ACEI's and ARBs. The primary side effect is diarrhea, which was seen in 2% of patients, usually on higher doses. Angioedema was also rarely noted. As with other drugs that affect the renin-angiotensin system, aliskiren should not be used during pregnancy. Aliskiren will be marketed by Novartis Pharmaceuticals, and will be marketed under the trade name Tekturna.

Alternate Treatment for Osteoporosis

Antiresorptive agents are standard therapy for osteoporosis. These drugs, which include the bisphosphonates (alendronate, risedronate, etc.) prevent bone breakdown, but they do not stimulate production of new bone. A new study looks at recombinant human parathyroid hormone (1-84) (PTH), a bone forming agent, as an alternative treatment for osteoporosis. In an 18 month, randomized, double-blind, placebo-controlled, parallel group study, 2,532 postmenopausal women with low bone mineral density at the hip or lumbar spine were randomized to receive 100 µg of PTH or placebo daily by subcutaneous injection. All received additional calcium 700 mg/d and vitamin D 400 U/d. The main outcome was new or worsened vertebral fractures, changes in bone mineral density as well as safety of the medication. PTH significantly reduced the risk for new or worsened vertebral fractures. The relative risk varied depending on the assumptions about women who did not complete the trial, but there was improvement in all subgroups. PTH also resulted in increased bone mineral density compared to placebo of 6.9% at the spine and 2.1% at the hip compared to placebo, but decreased bmd at the forearm. PTH also resulted in increased percentage of participants with hypercalciuria, hypercalcemia, and nausea by 24%, 23%, and 14% respectively compared to placebo. The authors conclude that parathyroid hormone (1-84) reduced the overall risk for new or worsened vertebral fractures in postmenopausal women with osteoporosis, and suggest that PTH provides an alternative therapy option for fracture prevention (*Ann Int Med.* 2006;146:326-339). This study adds a second option for anabolic (bone-forming) agents along with teriparatide.

Roche's Oseltamivir: Scrutiny, Bird Flu, and New Drug Applications

Roche's oseltamivir (Tamiflu) has come under scrutiny in Japan after 2 students who took the drug fell to their deaths in February. The drug has been associated with abnormal behavior in anecdotal reports including a Japanese boy who ran in front of a truck after taking the drug in 2004. Roche counters that influenza can cause abnormal behavior and denies a link between the medication and psychiatric problems. The drug has previously been associated with delirium, and the FDA has required labeling urging close monitoring for abnormal behavior since November 2006. Countries worldwide are stockpiling oseltamivir in case of avian influenza outbreak. Meanwhile Roche has filed a new drug application with the FDA for pediatric doses of the drug for children one year and older. The new capsules and a 30 milligram and 45 mg capsule would join the 75 mg adult strength capsule.

FDA Actions

The FDA has approved duloxetine (Cymbalta) for the treatment of generalized anxiety disorder. The drug is currently approved for the treatment of major depressive disorder in the management of diabetic peripheral neuropathic pain. The FDA approved duloxetine 60 mg once daily for the treatment of anxiety based on three randomized, double-blind placebo-controlled trials in 800 patients.

The FDA has approved lisdexamfetamine dimesylate capsules for the treatment of attention deficit/hyperactivity disorder in children age 6-12. Lisdexamfetamine is a pro-drug of dextroamphetamine that may be associated with less drug abuse than dextroamphetamine. The once-a-day drug will be available in 30, 50, and 70 mg strengths. Lisdexamfetamine is marketed by New River Pharmaceuticals under the trade name Vyvanase. ■