INTERNAL MEDICINE ALERT

Evidence-based summaries of the latest research in internal medicine

Providing Evidence-based Clinical Information for 36 Years

AHC Media Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com
www.cmecity.com

AHC Media

INSIDE

Financial Disclosure:
Internal Medicine Alert's editor, Stephen Brunton, MD, is a retained consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Lilly, Novartis, Novo Nordisk, Sanofi, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

What Is Our Current Understanding of Epilepsy Prognosis?

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD

Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Cornell Medical College

Dr. Kandula reports no financial relationships relevant to this field of study. This article originally appeared in the December 2013 issue of Neurology Alert.

Synopsis: *This paper summarizes and focuses on the National General Practice Study of Epilepsy with emphasis on epilepsy prognosis after initial diagnosis.*

Source: Shorvon SD, Goodridge DM. Longitudinal cohort studies of the prognosis of epilepsy: Contribution of the National General Practice Study of Epilepsy and other studies. *Brain* 2013;136(Pt 11):3497-3510.

Our current understanding of epilepsy prognosis stems from the cumulative data of large cohort studies published over the last few decades. In this paper, Shorvon and colleagues review the details of the National General Practice Study of Epilepsy (NGPSE), the first and largest prospective, population-based study of adults and children with epilepsy. The principal endpoint of the study was to describe the prognosis of newly diagnosed seizures with regard to seizure recurrence and remission and mortality. Secondary endpoints included treatment patterns and psychosocial aspects of epilepsy.

Patients for the NGPSE were prospectively recruited through 275 general practitioners (GP) within Great Britain from 1984-1987. At 6-month follow-up, patients were classified into febrile convulsions (220 patients), definite epileptic seizures (564 patients), and possible epileptic seizures (228 patients). Stratification was based on combined clinical information from the referring GP and selected adult and pediatric neurologists with epilepsy training. Of the 564 definite epilepsy cases, 346 were idiopathic/cryptogenic, 119 remote symptomatic, 83 acute symptomatic, and 16 with neurologic deficit. Cerebrovascular disease and stroke were the two most common symptomatic etiologies.

VOLUME 36 • NUMBER 2 • JANUARY 29, 2014 • PAGES 9-16

INTERNAL MEDICINE ALERT IS AVAILABLE ONLINE
www.internalmedicinealert.com

Patients were followed at 6 months and subsequently had annual evaluations over a median of 22 years.

Of the 564 patients with definite seizures, 67% and 78% had recurrence at 12 months and 36 months, respectively. Seizures associated with a fixed neurologic deficit from birth had 100% recurrence at 12 months in contrast to 40% recurrence from acute brain insults. In addition, those < 16 years or > 59 years of age also had a high risk of seizure recurrence (83%). Other factors associated with risk of recurrence included partial seizures (94%) vs 72% for generalized seizures. The rate of relapse was inversely related to duration of seizure freedom. The hazard rate for seizure recurrence or percentage risk of having a recurrence was 0.033 per week in the first 6 months after the first seizure, then fell to 0.007 per week at 6-12 months, and finally 0.004 per week in the next 24 months. The overall relapse rate at 3 years after the first seizures was roughly 75%, but 44% if no relapse in the first 6 months, 32% if no relapse after 12 months, and 17% if no relapse at 18 months.

In terms of remission, the number of seizures in the first 6 months after study notification (seizure density) predicted chance of remission. Hence, for an individual with two seizures during the 6-month period, the chance of making the 1-year remission rate was 95% and 47% for 5-year remission vs 75% and 24%, respectively, for individuals with high seizure density (≥ 10 seizures during the 6-month period).

For individuals with febrile convulsions, 6% of the children ultimately developed epilepsy (mean follow-up of 21.6 years). The standardized mortality rate (SMR; ratio quantifying the increase or decrease in mortality of a study cohort with respect to the general population) for patients with possible epilepsy was 2.5 vs 3 for those with definite epilepsy. The SMR was the highest at 5.1 during the initial year of diagnosis, then declined to 2.5 and 1.3 at 3 and 5 years, respectively. The SMR for those with idiopathic epilepsy was 1.6, remote symptomatic epilepsy 4.3, and acute symptomatic epilepsy 2.9. The authors concluded that the mortality rate was higher in those with newly diagnosed epilepsy largely due to underlying cause. Seizure recurrence and antiepileptic drug treatment did not influence mortality rate. At median follow-up of 22.8 years, SMR for those with definite epilepsy was 2.55, with pneumonia and cerebrovascular disease as most common causes of death.

In terms of treatment patterns, nearly 50% of those on treatment were in 5-year remission. Twenty-nine percent of patients with one or more seizures a week had never tried a second agent and only 23% had tried four or more antiepileptic drugs.

Using the Washington psychosocial inventory, a questionnaire was sent to 216 patients with an 89% response rate. The four major problem areas identified by patients were fear of seizures, fear of stigma in employment, adverse effects on leisure, and lack of energy. The conclusion of the questionnaire was that psychosocial impact was related to severity of the illness rather than the diagnosis itself.

■ COMMENTARY

Based on this longitudinal, prospective study, a few generalizations regarding epilepsy prognosis can be made. Overall, epilepsy has a good prognosis, with 65-85% remission rate. In particular, the long-term prognosis for febrile seizures developing into epilepsy in children was 6%. The likelihood of long-term remission is better in newly diagnosed cases rather than chronic cases. Early treatment response to seizures is an indicator of overall long-term prognosis. The longer the overall remission period, the less likelihood of subsequent seizure recurrence. In contrast, the longer the epilepsy is active, the prognosis is poorer. Remission periods followed by relapse were less common than initial active seizures with remission and no remission at all (refractory state). Epilepsy has the highest mortality rate in the initial years after diagnosis and appears to be dependent largely on underlying cause. Lastly, clinical factors predicting worse prognosis are presence of fixed neurologic deficit early in life, high seizure density before treatment, poor initial response to antiepileptic drug treatment, and certain epilepsy syndromes.

Perhaps the most puzzling question is why epilepsy prognosis continues to improve. Although it seems in-

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

EXECUTIVE EDITOR: Leslie Coplin.
MANAGING EDITOR: Neill L. Kimball.
EDITORIAL DIRECTOR: Lee Landenberger.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 550669, Atlanta, GA 30355.

Back Issues: $21.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

AHC Media

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: neill.kimball@ahcmedia.com
Online: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $349
Add $19.99 for shipping & handling.
(Student/Resident rate: $125)

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 45 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This enduring material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for up to 24 Prescribed credits by the American Academy of Family Physicians. AAFP certification begins January 1, 2014. Term of approval is for one year from this date with the option of yearly renewal. Each issue is approved for 1 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

tuitive that the ever-increasing clinical armamentarium of second- and now third-generation antiepileptic agents may have a large role in the matter, to date there have been no epidemiologic data to firmly support this hypothesis. In the future, an analysis comparing epilepsy prognosis in patients treated with first- and second-generation medications is warranted to thoroughly answer this clinical question. ■

Sometimes Coma Is Not a Coma

ABSTRACT & COMMENTARY

By Andrew Goldfine, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Goldfine reports no financial relationships relevant to this field of study. This article originally appeared in the December 2013 issue of Neurology Alert.

Synopsis: *Novel protocols with functional MRI may allow clinicians to determine if some unresponsive patients are able to hear, understand, and respond to questions.*

Source: Naci L, Owen AM. Making every word count for nonresponsive patients. *JAMA Neurol* 2013 Aug 12; doi:10.1001/jamaneurol.2013.3686 [Epub ahead of print].

VEGETATIVE STATE (VS) AND MINIMALLY CONSCIOUS STATE (MCS) are behaviorally defined as no interaction and minimal interaction with the environment, respectively. Of increasing concern is that patients with these syndromes may be misdiagnosed and actually have higher levels of consciousness than they demonstrate on exam, due possibly to fluctuating level of arousal or disproportionate damage to motor systems. Proper diagnosis is essential, as patients in MCS have a higher likelihood of recovery to independence than those in VS, and patients with full consciousness theoretically could communicate through brain-computer interfaces.

To bypass damaged motor systems, investigators have recently made use of brain imaging tools including functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), with the typical output being change in brain activity to a command. In *JAMA Neurology*, Naci and Owen report taking this approach one step further by developing a fMRI system to allow patients to communicate. This same research group previously reported a case of a VS subject who communicated through fMRI (imagine playing tennis for yes and navigating around your house for no), but here they report on an experimental paradigm that is more natural for a patient to perform.

In this study, subjects had fMRI performed while they listened to a voice say the words "yes" or "no" in alternate blocks of 22 seconds. These target words were interspersed with the numbers one through nine as distractors. At the beginning of each block, subjects were asked a question (e.g., "Is your name Steven?") and then told to attend to the word that answered the question.

To analyze the data, the authors compared brain activity during "yes" and "no" blocks. To narrow down where to look for a response, they first exposed the subjects to the same stimuli, but instead asked them to count the target words (yes/no) or just relax. The comparison of "count" to "relax" blocks revealed brain regions involved in attention, which were then used in the communication runs as "regions of interest" for analysis. This process allowed the authors to have subject-specific brain regions of interest, essential as these subjects had widespread brain injury and years of potential plasticity for recovery.

The authors report on one MCS and one VS subject who demonstrated evidence of communication — increased activation of attention-related brain regions during presentations of the correct answer (yes/no). In the MCS subject, the results were positive two out of four times, while in the VS subject results were positive four out of four times (two at one visit and two 5 months later). They do not report on other subjects they tested who may have had negative results.

■ COMMENTARY

This study offers a novel approach for detection of consciousness with some advantages and disadvantages to other approaches. Compared to the more standard task of motor imagery (e.g., playing tennis), this approach is more natural (attend to the word yes for a yes response) and does not require an intact motor imagery network (though like all existing approaches, does require language, thereby excluding subjects with aphasia). Their approach also has the advantage of subject-specific regions of interest, rather than requiring activation in brain regions developed from studies of healthy subjects. The primary disadvantage of this technique is that it uses fMRI, which is an inconvenient means of communicating with a potentially locked-in subject (though a positive result could justify further study with a bedside technology such as EEG).

The clinical implications of this and related studies are still not clear. This study and all others use convenience samples (highly chosen subjects), but to determine the prevalence of patients with positive responses as well as the prognostic significance, we need large-scale stud-

ies with randomly chosen subjects. Larger studies are also needed to know who is most likely to have a positive response, e.g., based on type of injury, clinical EEG, or imaging findings. Without this guidance, widespread implementation of these techniques may result in many false-positive or inconclusive results that could misguide therapeutic interventions. ■

Does Dietary Nicotine Protect Against Parkinson's Disease?

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is on the speakers bureau and advisory board for Allergan and Teva; speakers bureau for Boehringer-Ingelheim, GlaxoSmith-Kline, and Novartis; advisory board for Merz; and is a consultant for Gerson Lehman Group and Guidepoint Global. This article originally appeared in the December 2013 issue of Neurology Alert.

Synopsis: *This population-based, case-control study suggests that dietary intake of peppers and related species may be associated with decreased risk of Parkinson's disease. These plants are related to tobacco, raising the possibility that nicotine may be the underlying link.*

Source: Searles Nielsen S, et al. 2013 nicotine from edible *Solanaceae* and risk of Parkinson disease. *Ann Neurol* 2013; 74:472-477.

This case-control study evaluated risk of Parkinson's disease (PD) associated with dietary nicotine intake from edible plants of the *Solanaceae* family. A total of 490 newly diagnosed PD cases were compared with 644 controls. Of these participants, 63% of cases and 64% of controls were men, and mean age at the time of assessment was 66 years old (cases) and 68 years old (controls). Half of the PD cases and 62% of controls were classified as having significant history of smoking. PD cases were diagnosed by a movement disorders expert or by chart review by a team of neurologists at two centers in the Pacific Northwest. Edible *Solanaceae* family members studied were peppers, tomatoes including tomato juice, and potatoes (baked or mashed only), and nicotine intake associated with these was estimated based upon standard values for dry weight. A number of other non-*Solanaceae* vegetables also were evaluated. Logistic regression was used to calculate odds ratios with adjustments made for age, sex, race/ethnicity, non-*Solanaceae* vegetable intake, tobacco, and caffeine. Other potential confounders excluded were education, family history of PD, estimated alternative Mediterranean diet score, body mass index, and secondary smoking. The odds ratio (OR) for Parkinson's disease related to *Solanaceae* intake was 0.81 (95% confidence interval [CI], 0.65-1.01; *P*-trend = 0.07). However, by breaking down into different *Solanaceae* family members, this value was driven by intake of peppers (OR, 0.43; 95% CI, 0.24-0.78; *P*-trend = 0.005). For tomatoes, the OR was 0.83 (95% CI, 0.56-1.24) and for potatoes was 1.12 (95% CI, 0.73-1.7). Nicotine from eggplant intake was insufficient to meet the limit of quantitation. Not only were peppers associated with a lower risk of Parkinson's disease, an inverse association of PD risk with increasing pepper consumption was identified. For all participants, eating peppers 2-4 times weekly was associated with an OR of 0.7 (95% CI, 0.50-1.00), whereas the OR for daily intake was 0.5 (95% CI, 0.22-1.15). This inverse association was more pronounced in those who were not tobacco users.

■ COMMENTARY

Tobacco smoking has been associated with decreased PD risk in multiple studies, and nicotine has been suggested as the tobacco component responsible. This study addresses whether dietary intake of nicotine may have a similar association, and provides support for a link between risk of PD and dietary intake of edible plants of the *Solanaceae* family, which include peppers, tomatoes, potatoes, and eggplants, as well as tobacco. Not only does the study supports an association with dietary nicotine intake, but also a potential dose response, since the greatest risk reduction was associated pepper intake (highest nicotine content per kilogram of all the vegetables assessed here). Additionally results were more compelling in the subgroup of subjects who were not tobacco users vs those who were. All of this, therefore, supports a role for nicotine as at least one of the chemical compounds responsible for the inverse association of *Solanaceae* ingestion with PD risk. Moreover, nicotine possesses neuroprotective properties in the rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine animal models of PD. However, caution should be used in interpreting these results. Dietary data collection relies on subject self-report. Certain foodstuffs were not included, for example salsa or French fries. There is also first-pass metabolism in the liver that cannot be accounted for in such a study design. It is always challenging to discern which of an array of chemical constituents is/are relevant to risk modification. Peppers, in addition to containing nicotine, are excellent sources of nutrients previously found to be associated with lower PD risk, such as carotenoids, and also provide multiples

of the B vitamins and trace elements. Nonetheless, this study now provides independent support for a potential role of nicotine as neuroprotectant, and should stimulate further study as a potentially modifiable risk factor. It is, therefore, timely that an international clinical trial is now underway to examine the effect of transdermal nicotine administered in early PD. ■

Alcohol in Pregnancy

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora

Dr. Hobbins reports no financial relationships relevant to this field of study. This article originally appeared in the December 2013 issue of OB/GYN Clinical Alert.

Synopsis: *Data collected from a large study involving four countries show no effect of alcohol exposure in varying degrees on the rate of preterm birth, low birth weight, average birth weight, and preeclampsia.*

Source: McCarthy FP, et al. Association between maternal alcohol consumption in early pregnancy and pregnancy outcomes. *Obstet Gynecol* 2013;122:830-837.

A 2011 AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG) Committee Opinion gave "compelling and clear advice to avoid alcohol" in pregnancy and prior to pregnancy.[1] Yet the Centers for Disease Control and Prevention (CDC) indicates that about 50% of women in the United States admit to some intake of alcohol in pregnancy.[2] Since the data are inconsistent regarding how much alcohol affects the fetus, even in higher dosage, the Royal College of Obstetrics and Gynecology has taken a less conservative approach by saying that harm is unlikely to occur from one to two units of alcohol consumed once or twice per week.[3] However, the Royal College strongly advises against binge drinking.

In an effort to see if alcohol consumption in varying amounts has an effect on some easy-to-track outcomes, a multicenter study was undertaken in four countries: Great Britain, Ireland, New Zealand, and Australia — the Screening for Pregnancy Endpoints (SCOPE) study.[4] Outcome data were available on 5628 patients who were enrolled between 2006 and 2011. Patients were screened for alcohol consumption immediately prior to, and/or during, the first 15 weeks of pregnancy. The amount of exposure was quantified as follows: one unit of alcohol represented 10 mL of pure alcohol, which was equivalent to one shot of whiskey, a half a glass of wine, or one small glass of beer. Bottled mixed drinks each contained two units. Binge drinking meant that more than six units were consumed per drinking session.

The timing of alcohol exposure was broken up into four groups: 1) abstinent throughout this period, 2) none prior to conception, 3) quitting before 15 weeks, and 4) drinking throughout this window of time. Binge drinking was tracked according to these time intervals.

Based on the CDC data, the alcohol consumption statistics were not surprising. For example, 40% reported no alcohol consumption in pregnancy, 19% admitted to "occasional" intake (1-2 units per week), 25% were in the "low" category (3-7 units per week), 11% were "moderate" drinkers (8-14 units per week), and 5% were in the "heavy" group (> 14 units per week). Thirty-four percent said there was exposure to alcohol during the first 3 months and 23% admitted to at least one episode of binge drinking. It is important that the authors attempted to account for the many confounding variables, including smoking, when evaluating the results.

The authors studied four outcomes: birth weight, small for gestational age (SGA), spontaneous preterm birth, and preeclampsia. After adjusting for confounding variables there were no differences between groups regarding average birth weight, low birth weight, or the rates of SGA or preeclampsia. Even binge drinkers did not display differences in these categories and the timing of alcohol exposure had no effect on any of these endpoints.

Simply put, the timing and amount of alcohol consumption before and during early pregnancy seemed to have no effect on any of the four outcomes evaluated.

■ COMMENTARY

Often patients have been referred to us for ultrasound evaluations because they consumed alcohol in varying amounts early in pregnancy. The majority have not been hard-core drinkers and many were in the restaurant business where it is common for employees to gather at the bar for a few pops (or more) before heading home. Since the admonition to abstain from alcohol in pregnancy is well entrenched in the United States, these women were frightened out of their wits when they suddenly found themselves pregnant. This study suggests that their possible concerns, at least for preterm birth, growth restriction, and preeclampsia, can be allayed. On one hand, since alcohol consumption in large amounts during organogenesis can be a teratogen (the face and heart) and has the capability later in pregnancy to affect the central nervous system (as in fetal alcohol spectrum disorders), it would not be advisable to advocate a carte blanche approach to drinking in pregnancy, and obviously avoiding any alco-

hol is the best way to avoid any effect. On the other hand, since thus far there are no conclusive data to link modest intake with fetal effect, it is very unlikely that an occasional drink would have an adverse effect.

Many years ago, we tried to correlate alcohol intake in pregnancy with in utero brain findings on ultrasound, as well as with one specific measure of neurological performance in infants.[5] We found that abnormal neurological results correlated with frontal lobe size, which, in turn, correlated with alcohol intake. However, this relationship was significant only when there was heavy consumption (six drinks or more per day). Interestingly, no infant in the study, even in the high consumption group, displayed the constellation of stigmata necessary to document alcohol's most devastating effect — fetal alcohol syndrome.

The story gets more complicated on the maternal side when one delves into the genetics of vulnerability to alcohol addiction and the varying abilities of individuals to metabolize alcohol, and, obviously, on the fetal side there is much more to learn about alcohol's variable effects. Not surprisingly, the topic of alcohol in pregnancy is controversial and has brought out a full spectrum of hawks and doves (and last time I wrote about this I got flack from both sides). As indicated in the ACOG committee opinion, abstaining is a foolproof way to ensure that a fetus will not be affected. However, it also seems reasonable to tell women who have had some inadvertent exposure to alcohol in early pregnancy that it is unlikely to have had a major effect on their fetuses — with the caveat that it is time to either stop or keep their consumption to an occasional glass of an alcoholic beverage once or twice a week from that point on, as articulated by the British College. ■

References

1. American College of Obstetricians and Gynecologists; Committee on Health Care for Underserved Women. Committee opinion no. 496: At-risk drinking and alcohol dependence: Obstetric and gynecologic implications. *Obstet Gynecol* 2011;118(2 Pt 1):383-388.
2. Centers for Disease Control and Prevention (CDC). Alcohol use and binge drinking among women of childbearing age — United States, 2006-2010. *MMWR Morb Mortal Wkly Rep* 2012;61:534-538.
3. Royal College of Obstetricians and Gynaecologists. Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/RCOGStatement5AlcoholPregnancy2006.pdf. Accessed October 25, 2013.
4. McCarthy FP, et al. Association between maternal alcohol consumption in early pregnancy and pregnancy outcomes. *Obstet Gynecol* 2013;122:830-837.
5. Wass TS, et al. The impact of prenatal alcohol exposure on frontal cortex development in utero. *Am J Obstet Gynecol* 2001;185:737-743.

Pharmacology Update

Sofosbuvir Tablets (Sovaldi™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

THE FIRST NUCLEOTIDE ANALOG POLYMERASE INHIBITOR HAS been approved for the treatment of hepatitis C virus (HCV) infection. Sofosbuvir is marketed by Gilead as Sovaldi.

Indications

Sofosbuvir is indicated for the treatment of patients with hepatitis C infections (genotype 1, 2, 3, or 4).[1] This includes patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those who are coinfected with HCB and HIV-1 viruses.

Dosage

Sofosbuvir is taken once daily without regard to meals. For genotype 1 or 4, it is taken with peginterferon-alpha and ribavirin (PR) for 12 weeks. For genotype 2, sofosbuvir is taken with ribavirin only for 12 weeks and for genotype 3, 24 weeks.

Sofosbuvir is available as 400 mg tablets.

Potential Advantages

Sofosbuvir offers a low pill burden and the shortest duration of treatment to date (12 weeks total for genotype 1, 2, and 4). Sofosbuvir provides an interferon-free regimen for HCV genotype 2 and 3 and for patients with genotype 1 infection in whom interferon is not appropriate.

Potential Disadvantages

Anemia was reported in 21% of patients compared to 12% for PR.[1] Coadministration of enzyme-induced antiepileptic drugs should be avoided.

Comments

Sofosbuvir is a new class of anti-HCV drug. It is a nucleotide analog HCV NS5B RNA polymerase inhibitor. It differs from the previously approved non-structure protein protease inhibitors (boceprevir, telaprevir, and simeprevir). The efficacy and safety were evaluated in five phase 3 stud-

ies, one in treatment-naïve subjects with HCV genotype 1 or 4, three in various treatment-naïve and interferon-experienced HCV genotype 2 or 3 subjects, and one in subjects coinfected with HCV genotype 1, 2, or 3 and HIV.[1,2,3] One treatment-naïve study used an open-label design. Subjects infected with genotype 1 or 4 (n = 327) were administered sofosbuvir (400 mg once daily) with PR for 12 weeks.[1,2] The second was a noninferiority study. Those infected with HCV genotype 2 or 3 were randomized to sofosbuvir + ribavirin for 12 weeks (n = 256) or PR for 24 weeks (n = 243). The primary efficacy endpoint was sustained virologic response at 12 weeks after end of therapy (SVR12). SVR12 was 89% for genotype 1a, 82% for genotype 1b, and 96% for genotype 4. Overall, sofosbuvir was less effective in those with cirrhosis than in those without (80% vs 92%), and lowest in those with multiple factors, genotype 1, Metavir score F3/F4 fibrosis, non-CC IL28B, and baseline RNA > 800,000 IU/mL (71%). For treatment-naïve genotype 2 and 3 infected subjects, sofosbuvir + ribavirin was noninferior to PR overall. For genotype 2, sofosbuvir + ribavirin was more effective than PR (95% vs 78%) and numerically less effective for genotype 3 (56% vs 63%). Similarly, those with cirrhosis did not do as well. Two studies evaluated different durations of treatment (12, 16, and 24 weeks) with sofosbuvir and ribavirin in treatment-naïve and previously treated subjects. For genotype 2 infections, treatment longer than 12 weeks did not result in significant improvement in SVR12. For genotype 3 infections, the optimal dosing for sofosbuvir + ribavirin was determined to be 24 weeks. With 24 weeks of treatment of genotype 3 infections, SVR12 was 93% for treatment-naïve and 77% for treatment-experienced subjects. One open-label trial was conducted in subjects coinfected with HCV 1, 2, or 3 with HIV-1.[1] Genotype 2 subjects were given sofosbuvir + ribavirin for 12 weeks and genotype 1 and 3 subjects were given sofosbuvir + ribavirin for 24 weeks. Overall, SVR12 rates were 88%, 78%, and 92% for genotype 2, 1, and 3, respectively. Sofosbuvir is well tolerated; the treatment discontinuation rates were 2% for sofosbuvir + PR for 12 weeks, 1% for sofosbuvir + ribavirin for 12 weeks, and 11% for PR for 24 weeks.[1,2]

Clinical Implications

Sofosbuvir is the first nucleotide analog polymerase inhibitor to be approved for the treatment of HCV, and provides a treatment option for many HCV patients who have not been candidates for treatment previously. It is an option for all HCV genotypes and provides an advancement in the treatment of HCV infections. The wholesale cost for 4 weeks of SOF therapy is $28,000. ■

References

1. Sovaldi Prescribing Information. Foster City, CA: Gilead Sciences, Inc. December 2013.
2. Lawitz E, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; 368:1878-1887.
3. Jacobson IM, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013;368:1867-1877.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. ■

CME Questions

1. Which of the following is *NOT* true regarding the prognosis of epilepsy?
   a. Epilepsy associated with a neurological deficit at birth has a poor prognosis for cessation of seizures.
   b. The longer a person is seizure-free, the greater the likelihood that the person will remain seizure-free.
   c. Only 6% of children with febrile seizures will develop epilepsy.
   d. In general, epilepsy gets worse with the passage of time.

2. Which of the following statements regarding nicotine is *NOT* true?
   a. Nicotine in cigarette smoke is thought to reduce the risk of developing Parkinson's disease.
   b. Edible plants of the *Solanaceae* family, which include peppers, tomatoes, potatoes, and eggplants, contain variable amounts of nicotine.
   c. Nicotine appears to have neuroprotective effects.
   d. All of the above are true

3. Which of the following is true based on the findings in the SCOPE study?
   a. There was an increase in preterm birth in those with moderate-to-heavy consumption of alcohol.
   b. There was an increase in low birth weight in those exposed to alcohol.
   c. Binge drinking had an effect on fetal growth.
   d. There was an effect of alcohol on the incidence of preeclampsia.
   e. None of the above

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a retained consultant for Boehringer Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi.

Oral Fluoroquinolones and Retinal Detachment: False Alarm

Source: Pasternak B, et al. *JAMA* 2013; 310:2184-2190.

In the last decade, there have been numerous "scare signals" associated with medications: bladder cancer with thiazolidinediones, cardiovascular (CV) disease with rosiglitazone, acute blindness with PDE5 inhibitors, CV events with rofecoxib, tendon rupture with fluoroquinolones (FLQ), etc. Some early scare signals have ultimately proven correct, and others have not, including the recent retraction of CV warnings with rosiglitazone. Of course while we are grateful to be apprised of meaningful medication risks as early as possible, at the same time false alarms lead to unnecessary avoidance of treatments that might otherwise be the best choice in a particular situation.

A case-control study in 2012 reported a significant 4.5-fold increased risk for retinal detachment among persons prescribed FLQ vs not. Consistent with the prior experience of increased risk for tendon rupture with FLQ, it was theorized that ocular connective tissue disruption induced by FLQ could lead to vitreous and retinal detachment.

The frequency of FLQ prescription merits confirmation of the above-mentioned findings. To that end, Pasternak et al reviewed data from the entire population of Denmark from 1997-2011. In this interval, there were approximately 750,000 FLQ prescriptions (non-use control group = 5.5 million).

The data showed no statistically significant relationship between FLQ prescription and risk for retinal detachment. The authors suggest that if FLQ administration is associated with increased risk for retinal detachment, the risk is likely to be of negligible clinical significance. ■

PTSD May Impact Cognitive Function

Source: Cohen BE, et al. *J Clin Psychiatry* 2013;74:1063-1070.

The prevalence of posttraumatic stress disorder (PTSD) varies widely depending on the population studied. For instance, in the general population, the estimated prevalence is about 7%, but prevalence in veterans may be twice that much or greater. The direct effects of PTSD on quality of life are substantial, but there has been little scientific inquiry into whether PTSD causes other downstream consequences. Cohen et al in the Mind Your Heart Study (n = 535) have chosen to examine whether PTSD is associated with impairment of cognitive function by studying younger (age < 65 years) adult veterans free of known neurologic disorders. The investigators used the Clinician Administered PTSD Scale for documentation. Cognitive testing was performed with a battery that assesses multiple domains of cognitive function such as processing speed, working memory, and executive function.

Subjects with PTSD had worse cognitive performance in several areas: processing speed, executive function, and learning. CNS imaging has suggested that PTSD patients demonstrate anatomical reductions in the size of the hippocampus and frontal lobes, which are involved in episodic memory, processing, and executive function. Since depression, poor health behaviors, and vascular risk factors are also associated with cognitive dysfunction, the authors encourage particular attention to these elements in PTSD patients. ■

Electronic Cigarettes for Smoking Cessation

Source: Bullen C, et al. *Lancet* 2013; 382:1629-1637.

Despite their popularity, outcome trials for the efficacy of electronic cigarettes (eCIGs) — as well as long-term safety/efficacy data — are insufficient. The public, voting with their wallet, have widely endorsed eCIGs, if the fact that more than one-quarter of persons attempting to quit smoking in the United Kingdom in 2013 reported trying eCIGs is an adequate reflection of public sentiment.

Bullen et all performed a trial in New Zealand of adults expressing a wish to stop smoking (n = 657). Study subjects were randomized to an eCIG, placebo eCIG, or nicotine patch. Telephone counseling was available for additional support PRN. Smoking status (confirmed by exhaled carbon monoxide testing) was ascertained 12 weeks after the quit day.

Quit rates were low in all three arms of the study: 7.3% (eCIG), 4.1% (placebo eCIG), and 5.8% (nicotine patch). Because the quit rates were substantially lower than anticipated in the power calculation of the study, it was not possible to discern whether there was a statistically significant difference between the quit rates on "real" vs placebo eCIGs. In any case, the difference between them would hardly appear to be clinically relevant. There were no differences shown in serious adverse events, but considering the fact that eCIG use may potentially span many years, it would be premature to conclude that long-term use of eCIGs is safe. ■

In Future Issues:

Recommendations from the American Geriatrics Society Consensus Statement on Vitamin D for Prevention of Falls and Their Consequences