Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2015;17:121-2

Hot News

Caution with New Oral Hepatitis C Drugs

The hepatitis C field is living a revolution following the introduction of all-oral therapies that can cure most patients with short courses of direct-acting antiviral (DAA) combinations. Given that chronic hepatitis C affects globally around 20% of HIV persons, major attention has been focused on the HIV/HCV-coinfected population. Current evidence suggests that these patients depict cure rates of over 90%, similar to HCV-monoinfected individuals (Sulkowski, et al. JAMA. 2014; 312:353-61). Accordingly, current guidelines for hepatitis C therapy no longer separate mono- and coinfected subjects.

In Western countries, a large and growing proportion of chronic hepatitis C patients, including those with HIV coinfection, are older adults that suffer from other common comorbidities, including hypertension, diabetes, depression, dyslipidemia, etc., that require specific medications. On the other hand, treatment of hepatitis C in patients with advanced liver cirrhosis is being prioritized, and unexpected DAA toxicities could be unveiled in the real world as treatment prescription moves much wider from selected patients originally enrolled in clinical trials. In this regard, two case series reported recently highlighted that enthusiasm was unabated with DAA, but caution must be stressed with unrecognized side effects and/or drug interactions.

Bradycardia with sofosbuvir plus amiodarone

The FDA recently announced changes in the labeling of sofosbuvir to warn about a risk of serious and potentially fatal bradycardia when the drug is taken with the antiarrhythmic amiodarone. Symptomatic bradycardia was reported following initiation of treatment with sofosbuvir/ledipasvir or with sofosbuvir plus simeprevir or daclatasvir in nine hepatitis C patients already taking amiodarone (Ahmad, et al. Hepatology. 2015, in press). It occurred within 24 hours of starting hepatitis C therapy in six patients and within 2-12 days in three others. One patient died of cardiac arrest and three required pacemaker implantation. In three patients who continued taking amiodarone, rechallenge with ledipasvir (Harvoni®) or sofosbuvir (Sovaldi®) resulted in recurrence of symptomatic bradycardia. In another patient, rechallenge eight weeks after stopping amiodarone did not result in bradycardia.

The mechanism of this effect is unknown. However, the use of sofosbuvir without amiodarone has not been associated with significant bradycardia. The extremely long half-life of amiodarone (two months) means that when systemic availability of the drug is altered (new dose, change in absorption, or metabolic interaction) it would take six months before a new steady state is achieved. Thus, sofosbuvir would not be able to increase amiodarone levels fast enough to explain the sudden bradycardia in those patients. However, the opposite could occur: amiodarone likely increased sofosbuvir levels. Sofosbuvir is partially cleared via the p-glycoprotein (P-gp) transporter and amiodarone is a well-known inhibitor of P-gp. Thus, greater sofosbuvir exposures should be expected in patients taking both medications concomitantly. Of note, other drugs frequently used by cardiologists, such as diltiazem, verapamil, carvedilol, and dronedarone, are also P-gp inhibitors and might cause similar effects on sofosbuvir exposure and bradycardia (Wessler, et al. J Am Coll Cardiol. 2013;61: 2495-502).

On the other hand, sofosbuvir, like the anticoagulant dabigatran etexilate, is a prodrug that is subject to conversion by liver esterases, such as carboxylesterase 1 (CES-1) to its inactive metabolite, GS-331007. A single nucleotide polymorphism (rs2244613) that affects CES-1 results in lower dabigatran concentrations and reduced bleeding rates (Pare, et al. Circulation. 2013;127:1404-12). Up to one third of individuals harbor this single nucleotide polymorphism at chromosome 16 that hypothetically would increase sofosbuvir exposure.

Finally, sofosbuvir, but not GS-331007, is a P-gp substrate. A polymorphism at the ABCB1 gene (rs4148738) in chromosome 7 could impair the P-gp transporter activity, which may increase sofosbuvir exposure.

Altogether it seems that genetic predisposition along with concomitant prescription of P-gp inhibitors might increase sofosbuvir exposure, causing potentially life-threatening cardiotoxicity due to bradycardia (Fig. 1). The new sofosbuvir labels warn that the drug and amiodarone should not be taken concurrently. If concomitant use is warranted, cardiac monitoring in an inpatient setting is recommended for the first 48 hours. Daily monitoring of heart rate, either at home or in an outpatient setting, should continue for at least two weeks.

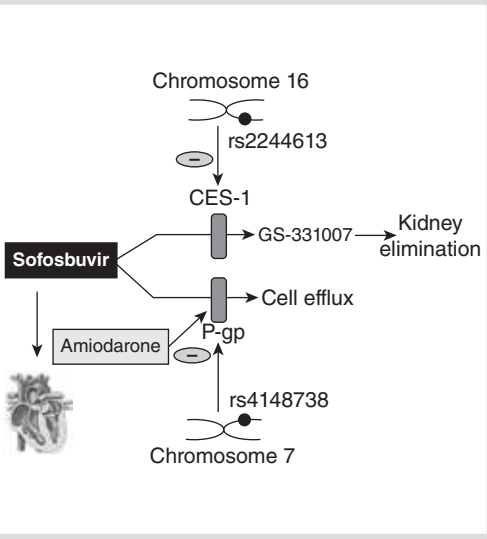

Figure 1. *Sofosbuvir and cardiotoxicity.*

Hepatic decompensation with simeprevir in advanced cirrhosis

Simeprevir (SMV) along with sofosbuvir has become a widely used combination to treat hepatitis C in patients infected with HCV genotypes 1 or 4. The drug package insert for SMV states that no dosing recommendation has been determined for patients with moderate or severe hepatic impairment, namely individuals with Child-Pugh B or C, acknowledging a lack of data in patients with advanced cirrhosis.

In HCV-uninfected individuals with Child-Pugh B and C cirrhosis, SMV concentrations increase 2.4-fold and 5.2-fold, respectively, with respect to healthy controls (Reesink, et al. Gastroenterology. 2010;138:913-21). Recent case series have reported individuals with Child-Pugh B that developed hepatic decompensation shortly (from four days to two weeks) after beginning sofosbuvir plus simeprevir combination therapy (Stine, et al. Dig Dis Sci., in press; and Soriano, et al. Antivir Ther., in press).

The mechanism by which SMV produced hepatotoxicity in these patients is unknown, but it was not associated with rash or photosensitivity, a dose-dependent side effect previously noticed in phase II clinical trials with simeprevir and other HCV protease inhibitors. Based on these observations, the updated AASLD/IDSA guidelines (www.hcvguidelines.org) recommend avoiding SMV in chronic hepatitis C patients with Child-Pugh B or C cirrhosis.

Vincent Soriano & Isabella Esposito
La Paz University Hospital & IdiPAZ
Madrid, Spain

New Update of the DHHS Guidelines for Adults and Children

On April 2015, the U.S. Department of Health and Human Services (DHHS) released an updated version of its antiretroviral treatment guidelines for adults. The new guidelines include revised recommendations for first-line antiretroviral therapy as well as management of treatment-experienced patients.

- There are now five recommended first-line regimens, including four integrase inhibitor combinations and one boosted protease inhibitor combination (darunavir/ritonavir) (see Table). Atazanavir/ritonavir and efavirenz regimens, previously classified as recommended, have been moved to the alternative category due to toxicities.
- Two interesting new sections have been incorporated. The first addresses central nervous system virological failure and new-onset neurological symptoms. In this regard, the inherent risk with protease inhibitor monotherapy is highlighted. A new section is focused on poor CD4 T-cell recovery and persistent inflammation and immune activation, as well as their role in increased risk of AIDS-related and non-AIDS morbidity. A new table outlining the mechanisms of antiretroviral drug interactions has been incorporated. A special mention is focused on those related to ritonavir- or cobicistat-boosted antiretrovirals, and on drug interactions with oral direct-acting antivirals for hepatitis C coinfection.
- The revised pediatric guidelines published on March 2015 include a discussion of very early treatment for HIV-infected infants. The updated recommendations address when to start antiretroviral therapy, now based on CD4 count rather than CD4 percentage. There is a new position for urgent antiretroviral treatment initiation for all children younger than 12 months and for older children with opportunistic illnesses or low CD4 counts. Lastly, there is the addition of integrase inhibitor-based regimens for children.

Pablo Labarga
Internal Medicine Department
La Luz Clinic
Madrid, Spain

Table 1. Antiretroviral therapy for HIV+ naive individuals

Recommended	Alternative
TDF/FTC + Dolutegravir	TDF/FTC + Efavirenz
ABC/3TC + Dolutegravir*	TDF/FTC + Rilpivirine#
TDF/FTC + Elvitegravir/c†	TDF/FTC + Atazanavir/c† (or r)
TDF/FTC + Raltegravir	TDF/FTC + Darunavir/c†
TDF/FTC + Darunavir/r	ABC/3TC + Darunavir/c† (or r)

TDF: tenofovir; FTC: emtricitabine; ABC: abacavir; 3TC: lamivudine; r: ritonavir; c: cobicistat.
*Only for patients with negative HLA-B5701; †Only for patients with creatinine clearance > 70 ml/min; #Only for patients with plasma HIV-RNA < 100,000 IU/ml.