Hepatitis C Treatment and Side Effects

January 4, 2016 By Lucinda K. Porter RN

People I encounter via email and the Hep Forum report a wide range of adverse events during hepatitis C treatment. Adverse events is the term used to describe potential side effects. These events aren't necessarily mentioned in the package insert that accompanies the prescription. Because Harvoni and some of the other direct-acting antivirals are new, we rely on post-marketing, real world experiences to better observe the possible side effects that people have.

Although I have heard quite a few complaints that aren't in the package insert, I don't assume they are side effects. If an adverse event occurs during hep C treatment, this isn't necessarily caused by the hep C medications. I'll illustrate this using data from two drug studies I read about recently.

Two subjects in hep C studies discontinued early because of anxiety attacks. Based on this information, one might guess that anxiety is a side effect of the experimental drug, and may be afraid to take it. However, if you continue reading, you would learn that the subjects discontinued on the first day of the study, and no other subjects reported intense anxiety. One might wonder it the anxiety was caused by fear of taking an experimental drug rather than by the actual drug.

However, when quite a few people report adverse events that don't show up in the package insert, I take note. For instance, people taking medications containing sofosbuvir (Sovaldi and Harvoni) occasionally ask if others are having heart rhythm abnormalities. The only reference to cardiac issues in Sovaldi and Harvoni's package insert is a post-marketing addition stating that bradycardia (a slow heart beat) has been reported in patients taking the drug amiodarone.

Heart rate and rhythm abnormalities are common, especially as we age. Many of those on hep C treatment are baby boomers, so statistically you'd expect this complaint to show up without assuming there is a causal relationship. That is, unless it shows up more than anticipated, and if the adverse event is discussed in the *New England Journal of Medicine* (NEJM) or other reputable scientific journal.

An editorial, "Bradyarrhythmias Associated with Sofosbuvir Treatment," was signed by twelve specialists from the Cochin Hepatology and Cardiology Group in France. (NEJM, Nov 5, 2015) They reported three cases of severe bradyarrhythmia that occurred during treatment with sofosbuvir plus daclatasvir, simeprevir, or ribavirin among 415 patients treated in their unit in 2014. Only one

of the patients was taking amiodarone. They do not say whether there were other milder cases of bradyarrhythmias. The editorial cites four arrhythmias in 1337 patients that were found in a safety investigation of the compassionate use of daclatasvir given with sofosbuvir in France, that lead to a warning by the French National Agency for Medicines and Health Products Safety.

The editorial concluded with, "*...the potential cardiac toxicity of sofosbuvir-containing regimens suggests the need for caution with the use of such regimens, including review of other medications, consideration of risk factors for bradyarrhythmias, and possibly monitoring of cardiac rhythm during the initiation of therapy*." (Note - Gilead's response disagrees with this.)

The differences between the European and U.S. information, made me wonder if there are differences between clinical trials results conducted in other countries. I decided to compare the adverse events listed in the package inserts from studies done in the U.S. and Canada. These two countries are somewhat demographically similar. Comparing 12 weeks of Harvoni, the discontinuation rate was less than one percent dropped out. That was the only similarity between the two countries.

The most common adverse events in the U.S. were fatigue (13%), headache (14%), nausea (7%), diarrhea (3%), and insomnia (5%). Less than 5% of subjects reported depression; less than 1% of subjects experienced suicidal ideation or suicide (data included sofosbuvir in combination with ribavirin or pegylated interferon/ribavirin. Adverse events that were added to the package insert after Harvoni was on the market were: "serious symptomatic bradycardia has been reported in patients taking amiodarone and skin rashes."

Compare this to the adverse events listed in the Canadian Harvoni package insert: headache and fatigue were also the most common, but these occurred only 4% and 2% respectively. All the other side effects were lumped in the less than 2% category. However, in that category, the list is long:

- **Blood and Lymphatic System Disorders**: Factor VIII inhibition
- **Cardiac Disorders**: Palpitations
- **Eye Disorders**: Visual impairment
- **Gastrointestinal Disorders**: Abdominal discomfort, abdominal distension, abdominal pain, constipation, diarrhea, dyspepsia, gastroesophageal reflux disease, mesenteric vein thrombosis, nausea, oral discomfort, vomiting
- **General Disorders**: Asthenia (weakness), feeling abnormal, irritability, edema
- **Hepatobiliary Disorders**: Hepatitis
- **Infections and Infestations**: Conjunctivitis infective, salpingitis, sinusitis
- **Injury, Poisoning and Procedural Complications**: Contusion, ligament sprain, meniscus

injury, muscle strain

- **Metabolism and Nutrition Disorders:** Abnormal loss of weight, decreased appetite, gout
- **Musculoskeletal and Connective Tissue Disorders**: Arthralgia, joint effusion, muscle spasms, muscular weakness
- **Nervous System Disorders**: Disturbance in attention, dizziness, memory impairment, migraine, migraine with aura, parosmia (smell distortion), somnolence (sleepiness)
- **Psychiatric Disorder**s: Affect lability, aggression, anxiety, depressed mood, depression, emotional disorder, insomnia, libido decreased, sleep disorder
- **Renal and Urinary Disorder**s: Urinary retention
- **Reproductive System and Breast Disorders**: Erectile dysfunction, metrorrhagia (menstrual bleeding irregularity)
- **Respiratory, Thoracic and Mediastinal Disorders**: Oropharyngeal pain, sinus congestion
- **Skin and Subcutaneous Tissue Disorders**: Acne, alopecia (hair loss), hyperhidrosis (excessive sweating), prurigo (itchy nodules), pruritus, rash
- **Vascular Disorders**: Hemorrhage, hypertension

It’s hard to believe these package inserts are for the same drug...

Discussions about side effects need to occur between patients and their medical providers. This is how real-world data is gathered. In addition to talking to your provider, report adverse events that are serious or not mentioned in the package insert to the FDA Adverse Event Reporting System. The more information that is collected the better.

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