In this month’s column of HCV Drugs I will discuss the two new approvals from the Food and Drug Administration (FDA)—Merck’s ZEPATIER and new indications for Bristol-Myer Squibb’s DAKLINZA to treat hepatitis C (HCV). This will be a short overview of both products. The information for this article is taken from the FDA Highlights of Prescribing Information and from the company’s press releases.

ZEPATIER

On January 28, 2016 the Food and Drug Administration (FDA) approved Merck’s ZEPATIER to treat HCV genotype 1a and 1b, and 4. ZEPATIER is a combination of two drugs elbasvir (HCV NS5A inhibitor) and grazoprevir (HCV protease inhibitor). The two drugs are combined into one pill taken once-a-day. ZEPATIER is taken for 12 or 16 weeks with or without food. Some patients will also have to take ribavirin. Merck has a patient assistance program to help with the cost of the medications.

Treatment Duration: People with genotype 1 and 4 are treated for 12 or 16 weeks.

Cure Rates: 90% to 100%

Resistance (RAVs): genotype 1a treatment naïve or genotype 1a pegylated interferon plus ribavirin treatment experienced patients with NS5A resistance (RAVs) will need to add ribavirin to ZEPATIER treatment.

Side Effects: The most common side effects include fatigue, headache, and nausea.

List Price: ZEPATIER is $54,600 for a 12-week course of treatment. This is substantially lower than 12-weeks of SOVALDI ($84,000), HARVONI ($94,500) and VIEKIRA PAK ($83,000). The list price may be negotiated with insurance companies, Medicaid and specialty pharmacies. It will be interesting to find out if this is a pricing game changer.

CONTINUED ON PAGE 2
Note: ZEPATIER was also approved in Canada. It was approved to treat genotype 1 and 4. ZEPATIER (plus sofosbuvir) is also approved to treat treatment naïve genotype 3 patients.

Patient Assistance Program: Merck has a patient assistance program for those who do not have insurance and co-pay assistance programs. A list of these programs and other information can be found in our A Guide to Understanding Hepatitis C: 2016. A link is provided at the end of this article.

DAKLINZA
On February 05, 2016 the FDA approved an additional indication for DAKLINZA. DAKLINZA is taken with sofosbuvir with and without ribavirin. It is taken with or without food. The updated label includes an approval to treat people with genotype 1 and 3 with HIV coinfection, people with cirrhosis, advanced cirrhosis and treatment of hepatitis C recurrence post liver transplant. BMS has a patient assistance program to help with the cost of the medicine.

Treatment Duration: 12 weeks

Cure rates:
- Genotype 1 and 3 HIV/HCV coinfection: DAKLINZA plus sofosbuvir—the overall cure rate is 98%-100%.
- Genotype 1 and 3 treatment of advanced cirrhosis and post-liver recurrence of hepatitis C infection: Daklinza, sofosbuvir and ribavirin—the cure rate is 50% to 92% depending on the severity of cirrhosis and genotype 1 subtype (1a or 1b). The cure rate for treating post-transplant recurrence of hepatitis C treatment is 95%.

Resistance (RAVs): In patients with genotype 1a with cirrhosis it is recommended that testing for the presence of the hepatitis C virus with NS5A resistance-associated polymorphisms.

Side Effects: The most common side effects of DAKLINZA and sofosbuvir are headache and fatigue. The most common side effects from DAKLINZA plus sofosbuvir and ribavirin include headache, anemia, fatigue, and nausea.

Cost: The list price of Daklinza is $63,000.

A Guide to Understanding Hepatitis C: 2016

RAVs
RAVs are resistance associated variants also called polymorphisms. RAVs can occur naturally before treatment in people who have never been treated, during treatment (viral breakthrough) and after treatment (treatment relapsers/failures/treatment experienced) with direct acting antiviral medications (inhibitors—protease, polymerase, NS5A). This can lead to a particular class of drugs (protease, polymerase, NS5A inhibitors) unable to inhibit a particular site of the virus.

A note about screening for RAVs: the presence of RAV’s to a certain class of drugs indicate that another class of drugs or another drug such as ribavirin may need to be added to the HCV drug cocktail. Another strategy is to extend the treatment duration. Many times another drug and extending the treatment duration is needed to overcome the ‘resistance’ of the polymorphisms.
Article: Treatment of hepatitis C virus–associated mixed cryoglobulinemia with direct-acting antiviral agents—M E Sise et al.

Study Aims and Results
HCV-related cryoglobulinemia is a disease that can cause severe consequences. Cryoglobulinemia produces cryoglobulin proteins that circulate in the blood that causes damage to various organs such as the skin and kidneys.

There has been a lack of information about the safety and effectiveness of treatment with direct-acting antiviral medications to treat cryoglobulinemia. The study compiled data from previous studies of twelve patients treated between December 2013 and September 2014 with simeprevir plus sofosbuvir or sofosbuvir plus ribavirin. Kidney biopsies or kidney function tests established cryoglobulinemia involvement in 7 patients. Fifty percent of the patients had cirrhosis. Four patients were also receiving rituximab (a drug used to treat non-Hogdkin’s lymphoma, rheumatoid arthritis, and cryoglobulinemia-related complications) while receiving direct acting antiviral therapy.

Conclusions
The overall hepatitis C cure rate was 83%. Eighty-nine percent of the patients who were cured of hepatitis C had a decrease in cryoglobulin levels. Four of the nine patients who had their cryoglobulin levels available for measurement had complete disappearance. Kidney function also improved after being cured. The treatment was generally well tolerated — there were only 17% with serious side effects.

Editorial Comment
This is good news for people with cryoglobulinemia. It is a disease with serious and potentially life-threatening consequences. The previous therapies that included pegylated interferon and ribavirin had many more serious side effects. If there was kidney involvement, ribavirin was often limited or dose reduced. Now that we have interferon- and ribavirin-free therapies we should be treating everyone with hepatitis C and cryoglobulinemia. Check out the article about cryoglobulinemia in this issue of the HCV Advocate. Also, follow this link to our new Extrahepatic Manifestation Glossary.

Now that we have interferon- and ribavirin-free therapies we should be treating everyone with hepatitis C and cryoglobulinemia.
Article: Increasing Prevalence of Cirrhosis among US Adults Aware or Unaware of their Chronic Hepatitis C Virus Infection—P Udompap et al.


Study Aim and Results
The aim of the study was to estimate the prevalence of cirrhosis in the United States in people who had already been diagnosed with hepatitis C and people who had not yet been diagnosed with hepatitis C. The authors used the National Health and Nutrition Examination Survey (NHANES) database. They tested people who were over 20 years old for HCV antibodies and follow-up HCV RNA (viral load) and determined the degree of fibrosis/cirrhosis. They also re-evaluated HCV positive people who had already been evaluated for cirrhosis.

Of the 52,644 NHANES people identified, 49,429 were tested for HCV, of whom 725 met the inclusion criteria of HCV RNA/viral load positive and had a fibrosis/cirrhosis measurement.

Conclusions
The percentage increase of cirrhosis and the number increase of Americans with cirrhosis:
- 6.6% in Era 1 (1988 – 1994) – 170,000 Americans
- 7.6% in Era 2 (1999 – 2006) – 190,000 Americans
- 17% in Era 3 (2007-2012) – 370,000 Americans

The increase in cirrhosis was due to increased age, diabetes, and obesity. The increase in the cases of cirrhosis was similar in the people who were already diagnosed and those newly diagnosed.

Editorial Comment
This study is alarming because the rise in the cases of cirrhosis is similar in the diagnosed and the newly diagnosed. Diagnosis and treatment of hepatitis C, diabetes and obesity could help curb the future prevalence of HCV-related cirrhosis, but time is rapidly running out.
The rate of spontaneous or natural clearance of the hepatitis C virus from the baby is about 25%, but interestingly it can occur for a child up to 6 years of age. The factors associated with natural clearance of HCV are IL28B (a type of HCV gene) and genotype 3. Children typically have mild to moderate HCV disease progression, and a child’s growth is similar to that of non-HCV infected children. It was also pointed out there are exceptions—some children do have accelerated HCV disease progression. Importantly, children typically have few extrahepatic manifestations or autoimmune diseases.

Editorial Comment
It must be heart wrenching to have a child infected with hepatitis C. In most instances treatment with pegylated interferon and ribavirin is not recommended unless a child has advanced HCV disease progression. There are on-going clinical trials with direct-acting antiviral medications that should be completed in 2016. Approval of direct acting antiviral medication to treat children infected with hepatitis C will bring some much-needed effective treatment and much-needed relief to their parents.

After the screening of blood donors, mother-to-child transmission (MTCT) of HCV has become the leading cause of pediatric infection, at a rate of 5%.
Cryoglobulinemia is a blood disorder caused by abnormal proteins in the blood called cryoglobulins. The cryoglobulins precipitate or clump together when blood is chilled then dissolve when rewarmed. The proteins can be deposited in small and medium-sized blood vessels which can lead to restricted blood flow to joints, muscles, and organs. The term frequently used is essential mixed cryoglobulinemia because the exact cause is unknown. There are three types of cryoglobulinemia – type I, type II and type III. Type I does not have rheumatoid factor activity whereas types II and III have rheumatoid factor activity. Rheumatoid factor is an antibody found in the blood of people afflicted with rheumatoid arthritis (a chronic autoimmune disease characterized by inflammation of the joints).

**HCV AND CRYOGLOBULINEMIA**
The relationship between HCV and cryoglobulinemia is believed to occur by way of the hepatitis C virus attaching itself to B lymphocyte cells, which causes the immune system to produce autoantibodies. The high prevalence of hepatitis C in people with cryoglobulinemia lends credence to the direct link between HCV and cryoglobulinemia. One study found that 90% of patients with type 2 or type 3 cryoglobulinemia had evidence of the hepatitis C antibodies.

Additionally, treating the underlying cause—hepatitis C—improves or resolves cryoglobulinemia further establishing the link. Also, cryoglobulinemia is associated with the hepatitis B virus and other liver disorders but to a much lesser extent.

Additional factors that strongly correlate with an increased risk for HCV-related cryoglobulinemia include the presence of cirrhosis, HCV infection over many years or decades, and female gender. In people with hepatitis C only about 3% of people with cryoglobulinemia show signs or symptoms of this condition. The other 97% of people with HCV and cryoglobulinemia have few symptoms or any of the blood or organ disorders associated with the more severe outcomes. It is important, however, to be monitored on a regular basis to make sure that the symptoms or disease progression does not worsen.

**Note:** Everyone with hepatitis C should be evaluated and receive HCV treatment. Current treatment is very expensive, and many insurance companies and Medicaid are restricting HCV treatment to people with the most severe HCV disease progression. One of the conditions that qualify people for HCV treatment is symptomatic cryoglobulinemia. Be sure to discuss any symptoms and conditions with your medical providers and have them included in your medical records. If you do not have insurance, you may qualify for free medications through the pharmaceutical patient assistance programs. If you have insurance, there are co-pay assistance programs. Resources are listed at the end of the article.
SYMPTOMS
People with symptomatic hepatitis C-related cryoglobulinemia can have ongoing problems that can cause many symptoms and disorders. The most common symptoms and complications associated with the cryoglobulinemia include:

Vasculitis: inflammation of the small blood vessels of the skin, kidneys, gastrointestinal tract and other organs of the body. It can also cause red or purple blotching skin that usually appears on the lower extremities of the body. Rashes, sores, and ulcers can also occur

Renal (kidney) disease: caused by deposits of the cryoglobulins in the kidneys. Symptoms include blood and proteins in the urine

Arthralgias and arthritis: pain and/or inflammation in the joints

Pruritus (itching): mild to severe

Fatigue: mild to severe

Pain: mild to severe

Lymph node enlargement: swollen gland-like tissue in the lymphatic vessels containing cells that become lymphocytes (white blood cells)

Peripheral neuropathy: numbness and tingling in the hands, legs and feet due to decreased blood and/or inflammation of the peripheral nerves

Stomach pain

Bleeding disorders: internal bleeding and abnormal blood clot formations

Non-Hodgkin’s lymphoma: (cancers of the lymphoid system)

Raynaud’s syndrome: a disorder that causes the blood vessels in the fingers, toes, ears, and nose to constrict or narrow causing pain

Multiple myelomas: cancer of the bone marrow and blood.

The more serious consequences of cryoglobulinemia usually occur after many years or decades of infection with the hepatitis C virus.

DIAGNOSIS
A simple blood test is performed to diagnose cryoglobulinemia, but the blood sample has to be handled carefully — drawing the blood sample at room temperature then cooling it to see if the blood precipitates or clumps together.

TREATMENT
The approach to treating HCV-related cryoglobulinemia is to treat the underlying cause — hepatitis C. Cryoglobulin disappearance, improvement in kidney function and complete or partial resolution of cryoglobulinemia syndrome occurs after successfully curing hepatitis C. The study reported in this issue of SnapShots demonstrates that direct acting antiviral medications are safe and effective to treat hepatitis C and cryoglobulinemia. Now that we have interferon- and ribavirin-free therapies the future of treatment for cryoglobulinemia and other HCV-related extrahepatic manifestations is bright.

Patient Assistance Programs
A guide to understanding HCV includes information about patient assistance programs.

The current drugs to treat hepatitis C have such high cure rates and minimal side effects (compared to the older therapies). This has created a dilemma for drug developers who must develop new drugs that somehow improve upon the current drugs. This is a difficult task, but not impossible. Probably the biggest achievement will be shorter treatment duration and lower cost. There is a percentage of patients who are the more difficult to treat, such as those with genotype 3 who have cirrhosis and have not achieved a cure with a previous course of therapy. The race is on for new, better and cheaper therapies—this is very good news for people living with chronic hepatitis C.

You will see below that the need for these new therapies has narrowed the pharmaceutical companies to a number that you can count on your fingers! As a result I have decided to rework our pipeline and list it by the pharmaceutical company. I am also just listing the major studies. This is also a new pipeline that will grow as information is released. The pipeline is a brief overview. More extensive information is listed in our newsletters and in our blog.

A brief overview of how this pipeline is laid out:

**Date:** The Pipeline will be updated on a monthly basis and will be included with the Mid-Month Newsletter

**Genotype (s):** This lists the drugs or combination of drugs and the particular genotype or genotypes that the drug is active against. I am not going to name the particular drug that works against one or all of the genotypes

**Comments:** This section will list the study results. Within this section, I will list the genotype(s) being studied and the phase of the study with a brief recap of the study.

You will note that many of the drugs or combinations of drugs are pan-genotypic—that is they work on many or most of the HCV genotypes. **Note:** Many of the drugs listed below have been updated with the latest information from the Liver Meeting 2015 and news reports as of 1/28/2016. More detailed information about drugs in development is available in our blog reported in the HCV Advocate newsletters.

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<tr>
<th>AbbVie</th>
<th>Genotype 1b</th>
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<td><strong>COMMENTS:</strong></td>
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<td><strong>Genotype 1b - Phase 3b Study:</strong> On January 7, 2016 the FDA granted Viekira Pak without ribavirin priority review status for people with compensated cirrhosis. The clinical trial to support the pending approval enrolled 60 patients and after 12 weeks of treatment the cure rate was 100%. The most common side effects were fatigue, diarrhea, headache and joint pain.</td>
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<tr>
<td>AbbVie</td>
<td>Genotype(s): 1, 2, 3, 4, 5, 6 (Pan-genotypic)</td>
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<td>COMMENTS:</td>
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<td>Genotype 1 – Phase 2 Study: ABT-493 (protease inhibitor) plus ABT-530 (NS5A inhibitor) with and without ribavirin in non-cirrhotic patients were treated for 12 weeks. The cure rates were 97-100% in genotype 1 patients; 96-100% in genotype 2 patients; 83-94% in genotype 3 patients. In a separate study of ABT-493 plus ABT-530 the cure rate was 97% in genotype 1 non-cirrhotic patients treated for 8 weeks. The combination of ABT-493 plus ABT-530 is currently in Phase 3 studies.</td>
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<tr>
<th>Achillion – Johnson &amp; Johnson (Janssen)</th>
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<td>• Genotype 1 – Phase 2 Study: ACH-3422 and Odalasvir (ACH-3102) and Sovaprevir are in studies with various combinations. Recently, Johnson &amp; Johnson Innovation – JJDC, INC (Janssen) made an investment in Achillion for co-development and distribution. See Janssen for a new study that features odalasvir.</td>
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<td>• Genotype 1 – Phase 2 Study: Odalasvir plus sofosbuvir (used as a proxy drug) to treat genotype 1 patients for 6 weeks achieved 100% (12 of 12 patients) cure rates. A proxy drug is a drug used to stand in for another drug. Sofosbuvir is a polymerase inhibitor so it is assumed that odalasvir plus a polymerase inhibitor that is being developed by Achillion will produce similar cure rates.</td>
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<th>Bristol-Myers Squib (BMS)</th>
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<td>• Genotype 1 – Phase 3: Unity-2 Phase 3: The combination of daclatasvir/asunaprevir/beclabuvir to treat 112 treatment-naïve and 90 treatment-experienced patients with compensated cirrhosis (DCV-TRIO) with and without ribavirin for 12 weeks. The average age was ~59 yo; mostly White males, HCV genotype 1a. The cure rates were 93% in the DCV-TRIO group (naïve-93%; experienced 87%) and 98% (naïve 98%; experienced 93%) in the DCV-TRIO group plus ribavirin. The most common side effects were headache, fatigue, nausea, and diarrhea. As expected the group that received ribavirin had more side effects.</td>
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### Gilead

**Genotype 1,2,3,4,5,6 (Pan-Genotypic)**

**COMMENTS:**
- **Genotype 1 – Phase 3:** Sofosbuvir plus velpatasvir (GS-5816) In Phase 3 clinical trials (ASTRAL-1-4), the cure rates in genotypes 1 through 6 ranged 97% to 100%. Gilead has applied for marketing approval to the Food and Drug Administration, (FDA) and approval is expected in 2016. The most common side effects were headache, fatigue, sore throat, runny nose, and nausea. **In January 2016 the combination received priority review status and Gilead stated that FDA approval is expected by June 28, 2016. To view the Phase 3 data go here:** [http://hcvadvocate.org/news/NewsUpdates_pdf/Advocate_2016/advocate0116_mid.pdf](http://hcvadvocate.org/news/NewsUpdates_pdf/Advocate_2016/advocate0116_mid.pdf)

- **Genotype 1 – Phase 2:** The combination of sofosbuvir, (velpatasvir), and GS-9857 given for 6 weeks to treatment naïve (never been treated) people who did not have cirrhosis cured 93% of people. **This combination is currently in Phase 3 studies.**

### Janssen

**Genotype 1,2,3,4,5,6**

**COMMENTS:**
- **Genotype 1 – Phase 1:** In a small study of samatasvir, it was found to be safe and have antiviral properties against genotype 1, 2, 3 and 4. There is now a phase 2 study of samatasvir plus Olysio (simeprevir) in treatment-naïve (never been treated) patients with genotype 1b or 4.

- **Genotype 1:** Janssen (Alios Pharma) has initiated a phase 2a study of AL-335, odalasvir, and simeprevir to treat HCV genotype 1 treatment naïve patients. There will be 60 patients divided into three treatment arms who are treated for 4, 6 or 8 weeks.

### Merck

**Genotype 1, 2, 3, 4, 6**

**COMMENTS:**
- **Genotype 1, 4, and 6 – Phase 3:** The combination of grazoprevir plus elbasvir (combined brand name Zepatier into one pill, once-a-day) to treat **genotype 1, 4 and 6** produced cure rates from 92% to 99%. The treatment duration was 12 weeks. The treatment was given Breakthrough Designation by the Food and Drug Administration. **The safety profile was excellent. ZEPATIER (grazoprevir plus elbasvir) was approved on January 28, 2016 to treat HCV genotype 1 and 4.**

- **Phase 2:** There were two studies – Part A: grazoprevir plus MK-3682 or elbasvir plus MK-3682 the cure rates for genotype 1a/b was 98%; Genotype 2 was 60-71%, but one group who received grazoprevir/MK-3682/MK-8408 had a 91% cure rate; Genotype 3 cure rate across all of the arms was 91%.
WHAT’S UP!

EASY C TREATMENT GUIDE
GENOTYPE 1

The first in a new series of Easy C guides about approved HCV direct acting antiviral medications to treat hepatitis C. The first guide is about genotype 1 treat options.

EXTRAHEPATIC MANIFESTATION GLOSSARY

We have just launched a new glossary of conditions linked to infection with the hepatitis C virus or conditions that are seen more commonly in people with hepatitis C. The glossary is our effort to help inform our audience to become aware of these conditions and seek medical care and treatment.

TATTOOS

Interested in tattoos? Visit our tattoo page for fact sheets, blogs and more…