Article: Retreatment with direct-acting antivirals of genotypes 1-3-4 hepatitis C patients who failed an anti-NS5A regimen in real world—P. Halfon, et. al.


Study Aims and Results
The goal of the study was to re-treat patients who had failed a first line course of therapy but who had developed treatment emergent NS5A drug resistance. There were a total of 2,995 patients in the group who were originally treated from January 2014 to March 2016. The patients were treated at six centers in France. A total of 80 patients (2.7%) relapsed. Of the 80 patients who relapsed, 24 developed NS5A resistance. The 24 patients were re-treated with a different combination of HCV direct-acting antiviral (DAA) medications. The patients were tested for HCV RNA (viral load) at week 4 and week 24 at the end of treatment (post-treatment).

At post treatment week 4 and week 24, 23 of the 24 patients were viral load negative (cured).

Conclusions
Retreatment of people who did not respond to a previous course of DAA therapy who developed NS5A drug resistance can be successfully retreated. In this study, retreatment with a different DAA combination achieved a 96% cure rate.

Editorial Comments
This is good news for the minority of people who do not achieve a cure with DAA therapy. We are very lucky to have such a variety of drugs to treat hepatitis C. We just need to make sure that everyone has access to these life saving medications.

1: To read the entire journal study that includes the NS5A drug combinations that failed and the retreatment drug combinations (includes genotype & fibrosis scores) http://www.journal-of-hepatology.eu/article/S0168-8278(17)32333-4/fulltext

“Real World Results” are treatment cure rates in the general hepatitis C population vs. cure rates seen in clinical trials—there can be significant differences because clinical trial participants are usually healthier people vs. real world populations that are people like you and me who have more health issues (such as diabetes, high blood pressure, obesity, more severe hepatitis C disease progression, kidney disease) and may not have the resources that patients have in clinical trials. In this study the “real world cure results” were 97.3%—now that is impressive!

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As for tinnitus, music and white noise can help, but ultimately, it just has to be accepted. It usually doesn’t go away. In this case, it might get worse because aspirin is the wrong thing to take when you have ringing in the ears.

So, back to our friend. This person was drinking for a bit, but stopped. The Forum posts showed that our friend was on the computer in the middle of the night, which is about the worst thing you can do if you have a sleep problem. The light from computer screens and handheld devices interferes with the brain’s sleep-wake cycle. The sleep-wake cycle is a delicate mechanism, and it doesn’t take much to mess it up.

The reason the person was drinking was from fear that the high cholesterol would cause a heart attack. Apparently, our friend didn’t realize that it is extremely common for people with hepatitis C to have low or normal cholesterol, get cured of hep C, and then have high cholesterol. One possible explanation is that hep C interferes with cholesterol production. Without fear of a cholesterol problem, people eat whatever they want. When hep C is gone, so is the cholesterol suppression.

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Our friend’s cholesterol was not dangerously high. It likely could be reduced with lifestyle changes. As for the daily aspirin, this is not advised unless medically recommended.

The bottom line is that sometimes we act as if we know more than doctors do. We search the internet, self-diagnose, and self-prescribe. But, here is what I’ve noticed about myself and others:

- I may think I know myself, but that may not be true, and it certainly doesn’t give me the license to practice medicine, even on myself.

- When we aren’t well, we get anxious and stressed. This is normal. If stress continues too long, our health may get worse.

- Fighting health problems can make matters worse. This is especially true for insomnia and tinnitus. I needed help for these problems.

- Taking action to be healthy is hard work. This is especially true when we don’t feel well because it means challenging ourselves when we are at our weakest.

Thinking about our friend, I recall those times when I was anxious, could not sleep, and didn’t trust doctors. The thought of exercise was foreign to me. Well-meaning friends suggested meditation, but I probably would have more success with learning how to swallow a sword than to sit still on a pillow. Eventually I got desperate enough to try meditation and exercise for a few minutes at a time. Those minutes grew into a regular practice.

Meditation is more than just a stress reduction tool; it is a tool for a health. In a recent study published in Clinical and Translational Gastroenterology, researchers reported that meditation-based practices can improve quality of life in patients with cirrhosis. It also can help our caregivers. In this study, couples were taught a technique known as mindfulness-based stress reduction (MBSR). Couples participated in four 1-hour group therapy sessions, and had improved health outcomes in just one month.

The cool thing about meditation is that there are no negative side effects. Yes, it is boring and your derrière muscles might get sore. Sitting and listening to your thoughts run around like squirrels on speed, can be irritating. However, in time, it pays off. Meditation costs nothing and the potential benefits are enormous.

Returning to our friend, the question is, would meditation help? Very likely. Meditation isn’t a cure, but it is a powerful tool to help us manage stress, sleep, pain, and symptoms from chronic illness. It’s a low risk-high benefit option available to all of us.

References:
- Hep Forums https://forums.hepmag.com

Lucinda K. Porter, RN, is a long-time contributor to the HCV Advocate and author of “Free from Hepatitis C” and “Hepatitis C One Step at a Time.” She blogs at www.LucindaPorterRN.com and HepMag.com
Did you know…

- Liver cancer is the third-leading cause of death worldwide; hepatocellular carcinoma, or HCC is the most common form of liver cancer. – Centers for Disease Control and Prevention
- 29,000 people will die from liver cancer in the United States in 2017. – American Cancer Society
- The most common cause of liver cancer in the United States is hepatitis C. – American Cancer Society

In this article, I will focus on hepatitis C-related liver cancer—the causes, symptoms, diagnosis, prevention, and medications to delay the eventual onset of death from liver cancer.

Liver cancer is the third-leading cause of death worldwide

What is Liver Cancer?

When a cell dies, an abnormal cell can take over the mechanism of the cell and grow out of control. The abnormal cells can form into cancer cells and grow into masses that can develop within an organ, can spread to nearby organs, tissues, lymph nodes and may transport themselves via the bloodstream throughout the body.

Hepatocellular cancer or hepatocellular carcinoma is the most common form of liver cancer.

Causes

The common causes of liver cancer in the United States include hepatitis C, fatty liver disease, hepatitis B, alcoholic liver disease, obesity, and diabetes. If you have more than one of these factors, it increases the risk of liver cancer especially once you develop cirrhosis. However, if you have chronic hepatitis B, you can develop liver cancer in the absence of cirrhosis. If infected with hepatitis C, liver cancer develops after severe fibrosis or cirrhosis has developed.

Symptoms

In early stages of liver cancer there are few symptoms. When symptoms appear they may include an ache (where the liver is located), fatigue, fever, and loss of...
appetite and feeling full (even after eating a small amount of food), vomiting, abnormal bruising or bleeding. Also, there may be some unexplained symptoms.

**Diagnosis**

People with hepatitis C with severe fibrosis or cirrhosis should be monitored on a regular basis for liver cancer. There are three main tests—alpha-fetoprotein test (AFP), liver biopsy, and imaging tests.

The alpha-fetoprotein test (AFP) is a chemical test that may be elevated in some people with cancer. The utility of the AFP is questionable since it is a not a very accurate test for gauging liver cancer. For instance, high levels of AFP are also present in pregnant women, other forms of cancer and may not show up as elevated for liver cancer.

Liver biopsy and imaging tests are better tools for diagnosing liver cancer.

The liver biopsy does have drawbacks because it can cause bleeding and the possibility of the biopsy needle hitting a tumor. A liver biopsy could pose a risk of ‘seeding the tumor’ or spreading cancer to other parts of the liver—although this belief is controversial.

Imaging tests are the preferred way to monitor for liver cancer. The American Association for the Study of Liver Disease (AASLD) recommends two forms of imaging—computed tomography (CT scan) and magnetic resonance imaging (MRI).

CT scan is a computer-generated image of multiple x-rays of the liver that can capture different angles. CT scans use radiation to generate images. MRIs are similar but use a different technology. Both diagnostic tests are safe. Both tests require an injectable contrasting agent (ink) that will highlight blood veins and cancer tumors (if any).

**Stages**

The most widely used liver cancer staging system is the American Joint Committee on Cancer (AJCC) TNM method. The system includes three categories:

- **T** for tumor – consists of the size and number of the tumor.
- **N** for lymph node – means the cancer has spread to lymph nodes.
- **M** for metastasis – cancer has spread to other parts of the body such as the lungs and bones.

The stages are numbered **0 to 4**: 0 is the least severe, and four is the most severe when it has spread to other organs.

**Prevention**

There are many strategies to prevent liver cancer. For people with hepatitis C, the best option is to treat and cure hepatitis C early before severe fibrosis or cirrhosis; this will eliminate further HCV disease progression and liver cancer. People with severe fibrosis or cirrhosis, who are treated and cured, will have a reduced chance of further HCV disease progression and liver cancer.

Important strategies to further reduce the risk of liver cancer include:

- Avoid alcohol – alcohol is another risk factor for liver cancer.
- Get vaccinated against hepatitis B (HBV) if not already immune – HBV is another risk factor for liver cancer. Get vaccinated against hepatitis A (HAV) to protect the liver from further infection.
If you have diabetes, keep it under control – diabetes is a risk factor for liver cancer.

Obesity is another risk factor for liver cancer. Talk with your medical provider about diet and exercise to combat obesity.

Fatty liver or NASH is another risk factor for liver cancer – diet and exercise may help. Hepatitis C can contribute to fatty liver—get treated and cured.

Early treatment of hepatitis C will prevent the development of liver cancer.

**Treatments**

There are various options to treat liver cancer—this is just a brief overview:

- **Resection (hepatectomy):** surgery to remove a single tumor in the liver of an otherwise healthy person. A resection will not be performed if the tumor invaded other parts of the liver or blood vessels.

- **Tumor ablation:** injections (alcohol, freeze or heat) to kill or reduce the size of the tumor.

- **Embolization:** places medications or synthetic materials into a blood vessel to block the flow of blood into the tumor to starve cancer.

- **Liver Transplantation:** This can be an option for some people with small liver tumors that have not spread to nearby blood vessels or organs.

**FDA Approved Medications**

There are three medications approved by the Food and Drug Administration (FDA) to treat HCC – liver cancer:

**Sorafenib Tosylate- brand name Nexavar:** (pills) in clinical trials Nexavar improved overall survival by 10.7 months compared to 7.9 months for placebo.

**Regorafenib-brand name Stivarga:** (pills) in clinical trials Stivarga improved overall survival by 10.6 months compared to 7.8 months for placebo. It is approved to treat people who have already been treated with sorafenib (Nexavar).

**Nivolumab- brand name Opdivo:** (infusion) is approved for patients who had previously been treated with Nexavar. In clinical trials, Opdivo improved overall survival by 3.2 months. The clinical trial was open-label – that is there was no comparator arm. People who continued on therapy for longer periods of time continued to respond to the treatment.

There is no cure for liver cancer unless someone is lucky enough to receive a liver transplant. Liver transplants are costly, and there is a shortage of available livers to provide liver transplants to all who need them.

*Note: There are three SnapShots articles on treating people with direct-acting antivirals (DAAs) and the risk of liver cancer in the October 2017 HCV Advocate newsletter.*


American Cancer Society
https://www.cancer.org

AASLD Practice Guidelines Hepatocellular Carcinoma

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**Alan Franciscus is the Executive Director of the Hepatitis C Support Project and the Editor-in-Chief of the HCV Advocate Website.**
From the fertile soil and clay cliffs of Kentucky, to the gently rolling landscapes of Indiana, that give way just beyond its borders to the seas of grass Laura Ingalls Wilder called home, I’ve been given an opportunity to change my perspective through experience. In a time when we seem to find letting our guard down and trusting each other difficult, I’ve found myself in rooms of people who are often drastically different yet all fighting every day for the same end.

Ten months ago, when I started this work with the HCV Advocate, I probably would have given you a more pessimistic outlook. I would have said we split ourselves into two groups, dug our feet into opposing mountain sides, and were unlikely to change. I was exhausted physically and mentally, and I was emotionally defeated. I had been in the middle of seeing people (on both sides) using facts and numbers as their ammunition. There was such a conviction in the certainty of the process, while having an unwillingness to see the obviousness of what’s in front of us. We will never be able to use two dimensional objects to accurately reflect the depth and breadth, and solutions for the problems faced by three-dimensional beings.

I’m happy to report I’m more fun to be around now (only a little though), and as I sit at a rest stop halfway between Maplewood, NJ and Atlantic City, I’m thankful for the opportunity Alan and the HCV Advocate gave me. More than anything, I’m grateful to all the training participants and communities that have welcomed us (and to those that we are headed to see). The contrast between places like Boston and Alabama, or the small mountain community of Franklin, NC and the bustling fast pace of Chicago is apparent.

Far less noticeable is how consistently, everywhere I go, people are willing to work together. For the time span of 5 or so hours we share a lot of information, we take quizzes and set plans of action for ourselves going forward. The real power of the training lies in the fact we increase the likelihood those plans we hold dear to us exceeding our expectations through meeting the other training participants, and creating new working relationships. Exceeding our own expectations and overcoming complex problems going forward means doing so together, without our egos.

In grade school, many of us are taught a fundamental truth about problem solving. A simple equation will need a simple solution. Proofs in geometry are more complex problems and they need not only longer explanations, but justifications for their answers. En route to the solution, you can write pages of reasoning and the logical steps needed to solve the problem.
This is a lesson we learn early, and one that stays with us throughout our lives. As we grow older and work with each other to solve larger problems, we begin to understand their solutions must follow the same path. Often though, the frustrations of problems incredibly close to us make it harder to hold to this understanding. On the surface, many people wouldn’t give my comment much thought. It is so basic that I think we often feel we don’t have to mention it. But if we go too long without actively reminding ourselves of this foundation, we run the risk of using it less and less, until we avoid using it altogether. We struggle, fail, gather ourselves and try again. Simple solutions that will solve a problem are exciting because they are easy to manage and are concrete. Wanting to find the simplest, most cost-effective solution to a complex problem isn’t a bad thing, but it must always be realistic and honest. There are some people who are driven and work vigorously with a single fixed viewpoint. This passion and advocacy are so strong that there are times when people will stand fiercely counter to those who disagree with them even slightly.

In some cases, any compromise or movement towards someone opposing viewpoint isn’t seen as a success for progress, but a loss. Somewhere along the line our strong values and beliefs have given way to an iron commitment for change to come from the other side. This happens to such a degree that at times we break down potential partnerships, while others are flat out avoided. If someone disagrees with us they are an “idiot” who doesn’t look at all the “facts.” While the other side may see them as “encouraging” the problem. And so, both sides, are held up on their courage and passion, but are anchored to their positions by ego, slowed and ultimately kept from progress.

The war we are fighting isn’t from individual mountainsides for the people who are in the trenches between us. It is only our perspective and frame of reference that leads us to see it that way. The intensity of debate can become so great that we forget the solution to our problems doesn’t need to be created from nothing. The solving of a single variable won’t bring an end to this; figuring out how to use what we have in ways that we didn’t realize will. And never forgetting that the war we are fighting is for our coworkers and neighbors, for those we stand in line with, and who help us at the bank; and far more often then we admit, sometimes, when we have the courage to look up, it’s who we see staring back at us in the mirror.

Matthew Zielske is the Training Manager for the Hepatitis C Support Project’s Train-the-Trainer workshop. He has a Master’s in Communication with a focus on health communication and health literacy.
The last of the drugs in development has been discontinued. Therefore we are discontinuing the HCV Monthly Pipeline Update. We will continue reporting any updates on HCV news in the HCV Advocate Newsletter, the HCV Advocate News & Pipeline Blog and the HCV Drug Pipeline and Conference Report.

<table>
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<tr>
<th>Merck</th>
<th>Genotype(s) 1, 2, 3, 4, 5, 6 (Pan-genotypic)</th>
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<td><strong>COMMENTS:</strong></td>
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<td>• Phase 2- AASLD 2016:</td>
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<td><strong>Merck has discontinued the development of these drugs</strong></td>
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**C-Crest:** The trial was a phase 2 study of a 3-drug co-formulation of MK-3682 (polymerase inhibitor), grazoprevir (protease inhibitor) plus ruzasvir (NS5A inhibitor) with and without ribavirin to treat HCV genotypes 1, 2 and 3. The treatment period was 8, 12 or 16 weeks. In the people who were previously treated with pegylated interferon plus ribavirin the SVR12/cure rates were 95% to 100% in genotype 1a, 1b and 3. In people with genotype 2 the cure rate was 87% in the 8-week group and a 100% rate in the 12-week group and 96% to 98% in the 16-week groups. There was very little difference in cure rates between the groups who had cirrhosis, and who did/did not receive ribavirin.

**C-Surge:** An on-going phase 2 study to treat people with genotype 1 who had failed a previous course of a direct-acting antiviral therapy (Harvoni or Zepatier) using MK-3682, grazoprevir and ruzasvir with and without ribavirin. In the group that received ribavirin the treatment duration was 16 weeks; in the group that did not receive ribavirin the treatment duration was 24 weeks. The cure rates were 98% (43 of 44 pts) in the 16 week group that received ribavirin and 100% (49 of 49 pts) in the 24 week group that did not receive ribavirin.
Janssen has discontinued drug development of this combination.

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<tr>
<th>AL-335 (mg QD)</th>
<th>ODV (mg)</th>
<th>SMV (mg QD)</th>
<th>HCV Genotype</th>
<th>Dosing Duration (weeks)</th>
<th>Number (%) with undetectable HCV RNA at SVR24*</th>
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QD: every day; QOD: every other day; RNA: ribonucleic acid; SVR: sustained virologic response. *All results SVR24, with the exception of genotype 3 which is SVR12 **One patient did not attend SVR12 follow-up.

Note: The two drug combination of odalasvir and AL-335 for a treatment duration of 8 weeks will not proceed into phase 3 clinical trials. Clinical trial development of the combinations to treat HCV genotype 3 will also not move forward.

The combinations were generally safe and well-tolerated.

The next phase of development is to study these combinations in phase 2B studies.
CHILDREN AND HCV

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- Find answers and accountability to get the results you want.
- Use the tools and guides we send you to track your progress.

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Mother-to-Child Transmission

The risk of mother-to-child transmission is approximately 5%. Some factors may increase the likelihood of transmission from a mother-to-child such as fetal scalp monitoring, birth by cesarean, high viral load (HCV RNA), coinfection with HIV. At this time there have not been any studies as fetal scalp monitoring, birth by cesarean, high viral load (HCV RNA), coinfection with HIV. At this time there have not been any studies

In children and adolescents infected with chronic hepatitis C in the United States. According to the National Examination Survey (NHANES) 2011-2013, 3% of adolescents and 0.5% of children had chronic hepatitis C. Worldwide it is estimated that there are 5 million children infected with hepatitis C.

We have updated a few Fact Sheets for you.

1. How to Tell Children They Have Hepatitis C
2. Hepatitis C in Children

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The HCV Advocate offers information about various forms of intervention in order to serve our community. By providing information about any form of medication, treatment, therapy or diet, we are neither promoting nor recommending use, but simply offering information in the belief that the best decision is an educated one.

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