Summary

Chronic hepatitis C virus (HCV) infection affects approximately 300 million people worldwide and currently is the most frequent cause for liver transplantation in the United States and Europe

Natural history studies suggest that up to 20% of chronic HCV patients develop liver cirrhosis after 20 years of infection. Moreover, the incidence of chronic liver failure is expected to increase over the next 10 years as a result of the "silent epidemic" of HCV infection

The recommended treatment for patients with HCV genotypes 1 and 4 is pegylated interferon plus ribavirin for 48 weeks. Such treatment has yielded overall sustained viral response (SVR) rates of 54-63% in randomized controlled phase III clinical trials. However, treatment responses are not uniform across all populations, and are dependent on various viral and host factors.

Treatment of patients with chronic hepatitis C virus (HCV) infection remains suboptimal, with the current pegylated interferon (PEG-IFN) and ribavirin combination therapy providing sustained viral response (SVR) rates of 54 - 63%. The aim of this study is to identify clinical, laboratory and histological findings that can predict non-response to this treatment.

The aim of treatment in chronic hepatitis C is to achieve a sustained virologic response (SVR) defined as undetectable HCV RNA with a sensitive PCR assay (<50 IU/ml) 24 weeks after the end of antiviral therapy. In patients who achieved an SVR following standard interferon (IFN)-based antiviral therapy, virological relapse

after 5 years of follow-up was observed in 2– 4% only, and no relapse was reported after 5–10 years. Moreover, the 5-year durability of an SVR was in excess of 99% in patients treated with pegylated (PEG) IFN. A number of host and viral factors have been identified that influence treatment outcomes.

Treatment predictors are important tools for the management of therapy in patients with C virus (HCV) infection. For the current standard treatment with pegylated interferon alfa and ribavirin in patients with chronic hepatitis C, infection with HCV genotypes 2 and 3, baseline viral load below 400,000–800,000 IU/ml, Asian and Caucasian ethnicity, younger age, low GGT levels, absence of advanced fibrosis/cirrhosis, and absence of steatosis in the liver have been identified as independent pretreatment predictors of a sustained virologic response. After initiation of treatment, initial viral decline with undetectable HCV-RNA at week 4 of therapy (RVR) is the best predictor of sustained virologic response independent of HCV genotype.

HCV Treatment: Predictors of Treatment Response:

It is well-known that there are many factors that affect a successful treatment outcome. When people are trying to make a decision about whether or not to be treated it is important to take many of these

Predictors of treatment response into consideration.

However, it is also important to remember that the predictors to treatment response listed below are there to help guide people in the decision making process; they should never be used to deny or discourage treatment for anyone. Also, just because someone does

not fall into these categories, it doesn't mean that they will not have a successful treatment outcome. Many people who have achieved a successful treatment outcome do not fall into any of these categories. There are also other reasons to be treated besides the goal of eradicating the hepatitis C virus. There is a growing body of evidence that suggests that treatment will help reduce liver inflammation, may reverse liver damage (scarring) and slow down disease progression. All of these factors are important reasons to seek HCV medical treatment.

Another important step when considering treatment is to review the data on treatment response of the two pegylated interferon and ribavirin combination therapies and partner with a medical provider to make the best possible treatment choice. Part of this process is analyzing the data based on genotype and viral load.

Genotype

Genotype is the most important predictor of a successful treatment response and also dictates the dose of ribavirin and length of therapy. People with genotype 1 have about a 50% chance of successful treatment (treatment period is usually 48 weeks) and people with genotypes 2 or 3 (treatment period is usually 24 weeks) have about an 70-90% chance of a successful treatment response, defined as elimination of HCV RNA. In addition, people with genotypes 2 or 3 are prescribed a lower dose of ribavirin than people with genotype 1.

HCV RNA or Viral Load

The viral load is an important determinant of treatment response. The lower the HCV RNA (viral load) the better the chance of eradicating the hepatitis C virus.

Low viral load: under 800,000 IU/mL

High viral load: over 800,000 IU/mL

Some recent studies have suggested that the cut-off between low and high viral load may be set too high.These studies have shown that people with a viral load under 400,000 IU/mL respond better to current medications compared to those who have a viral load above 400,000 IU/mL. More data is needed to confirm these observations.

Age

Age is a contributing factor to treatment outcome. Generally, people under 40 years old respond better to current HCV treatments than people over 40 years old.

This is due to a couple of reasons – the immune system of someone who is younger is more intact and better able to help with the task of fighting HCV. Also, the longer that one has hepatitis C, the more the virus can replicate and possibly cause damage to the liver, both of which are negative predictors to treatment response. This is why some medical providers now believe that people should be treated early on – before any liver damage has a chance to occur.

Gender

In general, women seem to respond better to current HCV edications than males. The reason for this is unclear, but some

experts believe that women (especially pre-menopausal women) can fight off the virus because of the positive effects of estrogen.

Disease Severity

The more the liver is damaged or scarred the less likely it is that people will respond to current HCV medications.

Race

In general, Asians tend to have the highest response rates to current HCV medications followed by Caucasians and African Americans. The reason for the lower treatment response rates of African Americans is unknown, but studies have ruled out factors such as adherence and/or socio-economic issues as the reason. Studies are underway to determine the reasons for the lower treatment response.

Metabolic Disorders

There are several conditions that decrease the chances of responding to HCV therapy such as insulin resistance, obesity, metabolic syndrome, and steatosis:

• **Insulin resistance** occurs when the pancreas produces and releases insulin after a meal so that cells can absorb and convert glucose (carbs/sugar) into energy. In an individual with insulin resistance the normal levels of insulin do not trigger the absorption of glucose into cells, leading to an excess of glucose in the bloodstream. It is further complicated as the pancreas makes and releases more insulin in response to the elevated glucose levels.

• **Obesity** is defined via certain measurements, such as BMI (body mass index), waist circumference and the measurement of actual

body fat. Studies have found that people who are obese do not respond as well to HCV medications as those who are at a healthy weight.

• **Metabolic Syndrome** is a group of conditions or risk factors (high blood pressure, obesity, elevated triglycerides, decreased HDL cholesterol) that increase the chances of developing heart disease, stroke and diabetes. In some studies it has been found that people with HCV and metabolic syndrome do not respond as well to current HCV medications.

• **Steatosis** is defined as fatty liver or fatty infiltrates in the liver. Steatosis can speed up disease progression and lower treatment response. There are no drugs to treat steatosis at this time, but some good strategies to reduce or control steatosis are to maintain a healthy lifestyle by eating healthy and nutritious foods, and to balance the amount of food consumed with regular exercise. Alcohol can also contribute to steatosis.

On Treatment Predictors

Adherence:

It is not surprising that taking all of the prescribed medications is a factor in treatment response. It has been found that adherence to the ribavirin dose during the first 12 weeks of treatment is particularly important in achieving an SVR. However, it is sometimes difficult to remember to take the medications all of the time and serious side effects may require dose reductions of the medicines. This is why it is so important to manage any side effects as soon as they occur before they become so severe that a dose reduction or discontinuation of therapy is required.

Summary

Rapid and Early Virological Response

Studies have found that rapid virological response (**RVR**) and early virologic response (**EVR**) are other important predictors of a successful treatment response.

RVR is defined as becoming HCV negative after 4 weeks of treatment. **EVR** is defined as having a 2 log drop in viral load (example: 1,000,000 IU/Ml to 10,000 IU/mL) after 12 weeks of treatment, and **cEVR** (complete EVR) is defined as undetectable HCV RNA (viral load) after 12 weeks of treatment, which will lead to a better chance of achieving a SVR.

Alcohol

People who drink alcohol while undergoing HCV therapy have a lower chance of achieving a successful treatment outcome.

The predictors to treatment response listed above can greatly affect treatment response and overall liver disease progression. Some of these predictors, such as genotype, viral load, age, race, gender, and disease severity, can not be changed. Other factors are within the realm of change by lifestyle modification. Starting and maintaining a healthy lifestyle that includes a diet and exercise program can be very difficult and challenging. Anyone with HCV should work closely with a medical provider to design a healthy nutrition and exercise program tailored to his or her individual needs.