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Canadian Society of Intestinal Research

Hepatitis C

The Liver

The liver is the largest solid internal organ and it is located underneath the ribcage in the right upper part of the abdomen. Although liver size depends on a person's age, body size and shape, gender, and disease state, in most adults, it is about the size of a football. The liver has many important functions. It acts as a filter for the blood. It metabolizes nutrients and other substances such as medications. It stores energy. It synthesizes proteins that are essential for our body to function, including those that help the blood to clot when we bleed. Although the liver is a very resilient organ that has the ability to repair itself, it is susceptible to damage from many different sources, including viruses, toxins, inherited conditions, and even our body's own immune system.

Hepatitis C

Hepatitis C is one of many viruses that can damage the liver. It affects more than 170 million people worldwide. In Canada, more than 350,000 people are living with this condition. Infection begins as acute hepatitis C, and although some will go on to clear the virus on their own, most people – approximately 75% – will go on to develop chronic hepatitis C.

Hepatitis C infection, whether acute or chronic, will often be silent. This means that diagnosis for many people could occur at the time of routine screening or as part of investigating the cause of other abnormal lab tests.

Although acute hepatitis C usually passes without consequence, in those who go on to develop chronic hepatitis C, years of infection may result in significant damage to the liver. To help those with the condition, we must identify those at risk and offer treatment when possible.

Hepatitis C is a curable disease.

Spreading Hepatitis C

Hepatitis C is transmitted through activities involving blood-to-blood contact. The most common risk factor is intravenous drug use, or sharing of other drug paraphernalia that may have contamination with blood, whether past or current. Although having had a blood transfusion before 1992 remains an important risk factor, with current screening practices for blood donors, the risk of acquiring hepatitis C from a transfusion today is exceedingly low. Other important risk factors include sharing personal hygiene items such as razors and toothbrushes with another person who is infected and piercings and tattoos done without appropriate sterilization. The risk of sexual transmission is low. You don't transmit Hepatitis C through hugging, kissing, or sharing eating utensils. Although research is in progress, there is no effective hepatitis C vaccine at this time.

Symptoms

Many people with hepatitis C do not have any symptoms, but for those who do, symptoms are generally nonspecific, such as mild fatigue or discomfort in the abdomen. Over many years, the inflammation in the liver caused by the hepatitis C virus may result in the formation of scar tissue. If very advanced, the amount of scar tissue in the liver may reach a level termed cirrhosis. Cirrhosis refers to a specific pattern and degree of scar tissue in the liver. For patients with cirrhosis, ongoing damage to the liver may eventually result in signs and symptoms such as worsening fatigue, fluid accumulation in the abdomen (ascites), bleeding from veins in the esophagus or stomach (varices), and confusion (encephalopathy). People with hepatitis C and cirrhosis are also at an increased risk of liver cancer.

The goal in identifying and treating hepatitis C is to cure the disease before cirrhosis and its complications occur.

Diagnosis and Screening

Testing to identify whether antibodies to the hepatitis C virus (anti-HCV) are detectable in the blood reveals that the person either has a current or past infection. If this test is positive, a test to look for the presence of the virus in the blood (HCV RNA) should be done to determine whether a person is currently infected.

Screening for hepatitis C is recommended for people who have one or more of the risk factors described above and/or abnormalities in liver enzyme tests. Other people may benefit from testing; if in doubt, ask your health care provider.

Types of Hepatitis C

The hepatitis C virus exists in many different forms, which differ based on their genetic codes. The different types of hepatitis C are known as genotypes. These genotypes number from 1 to 6. Each genotype may have other subtypes, denoted by a lower case letter (e.g., genotype 1a). The genotype is important because it determines the approach to treatment. Genotype distribution varies based on geography and in North America, the most common genotype is 1, followed by genotypes 2 and 3. The hepatitis C viral genotype can be determined using a blood test.

Investigations

When a person receives a new diagnosis of hepatitis C, it is important that he or she sees a health care provider with specialized knowledge in the area. This may be a nurse, family doctor, or specialist (hepatologist or gastroenterologist). Initial investigations will help to determine the genotype of disease, rule out other underlying causes of liver disease, and to determine the extent or stage of the underlying disease. Most of this information can be obtained through physical examination, blood tests, and imaging of the abdomen (usually ultrasound).

Determining the degree of fibrosis (scar tissue) in the liver (also known as staging) can provide important information for the person affected by hepatitis C as well as their health care provider. In the past, staging was accomplished only by liver biopsy. Liver biopsy involves the use of a needle to take a sample of liver tissue for examination under a microscope. Although biopsy is a safe procedure, it is an invasive one, and thus does carry some risks, including bleeding and post-procedure pain. One of the drawbacks of liver biopsy other than its invasive nature is the fact that it samples only a very small portion of a large organ, and thus is susceptible to sampling error.

Non-invasive Tools to Measure Fibrosis

Liver biopsy remains the gold standard for the staging of liver disease and it is still a good option for many patients. However, health care providers are increasingly using other effective tools to determine the degree of fibrosis in the liver. Of the emerging alternative staging methods, the following are the most commonly used in Canada.

FibroScan® is a non-invasive tool used to assess the degree of fibrosis in the liver. It is a technique used to measure liver stiffness, which is closely related to the degree of fibrosis in the liver. The scan involves the painless placement of a probe on the surface of the skin, and takes only a few minutes to complete. The area sampled is approximately 100 times that seen on a typical liver biopsy. This procedure results in a reliable reading for most people. FibroScan® is available at a number of centres across Canada.

FibroTest and APRI (AST-to-Platelet Ratio Index) are non-invasive tools that rely on calculations based on blood tests to measure the degree of fibrosis in the liver. FibroTest is likely not covered by medical plans and therefore will have associated out-of-pocket expenses. APRI is derived from a calculation using a simple equation based on common blood tests.

Regardless of the tool used to estimate fibrosis, expert interpretation is essential in ensuring the information gained is useful in making treatment decisions. In addition, liver biopsy may still provide valuable information regarding disease activity that non-invasive tools cannot. Your health care provider will be able to determine which tests are best suited to your situation.

Management

The goal of hepatitis C treatment is to cure the disease. Achieving this goal requires a commitment to success from both patient and health care provider.

Pre-Treatment Management

Taking steps to minimize the risk of disease progression and optimize the chances of success once therapy begins are integral to achieving cure in the management of chronic hepatitis C.

Alcohol

Excessive alcohol consumption is a known risk factor for disease progression. While a safe level of alcohol consumption is difficult to accurately define and may differ from person to person, limiting intake to no more than 1-2 drinks per day (one drink is 5oz of wine, 1.5oz of spirits, or 355mL of beer) and not consuming alcohol every day is a reasonable goal. Those with more advanced liver disease might need to limit intake to a

greater degree or even abstain from alcohol. Discuss this issue with your health care provider.

Metabolic Risk Factors

Elevated fasting blood sugar and elevated body mass index (BMI) are factors that may decrease the chance of cure. Thus, a healthy diet and lifestyle, including optimal management of underlying medical conditions such as diabetes prior to starting treatment, might further increase the chance of success.

Depression and Other Mood Disorders

Treatment for hepatitis C may be associated with a number of side effects, and coping with them can be stressful. In addition, the medications themselves may have a direct effect on mood, including feelings of depressed mood and irritability. For these reasons, stable control of any pre-existing mood disorder and good social supports are very important.

Other Medical Conditions

Pre-existing ischemic heart disease, seizure disorders, and blood disorders will not necessarily prevent treatment, but physicians may need to address them prior to embarking on therapy. It is important to have a detailed discussion regarding your medical history with your health care provider as part of treatment planning.

Herbal Therapies

Significant interest exists in herbal preparations that may influence the severity of disease and improve quality of life in hepatitis C. To date, none of these types of preparations have conclusive evidence to recommend their use. Even what is perhaps the most widely used agent, oral milk thistle (or its active extract silymarin), does not have sufficient evidence to suggest benefit, despite research in a well-designed randomized control trial.

Curative Therapies for Hepatitis C

Current therapy to cure hepatitis C relies on medications taken for between 8 and 48 weeks. The duration of therapy and the specific regimen depends on the particular patient and the viral genotype. Recent advancements in hepatitis C therapies have boosted cure rates to greater than 90% for the vast majority of individuals. Remarkably, tolerability has also improved dramatically, and treatment durations are becoming shorter and shorter. Ongoing research will eventually ensure exceedingly high cure rates for all. The following is an overview of current therapies.

Pegylated Interferon

Interferons are a family of proteins that are released by the body's cells to help fight off viral infections. Researchers have long known that giving additional interferon to people infected with hepatitis C can boost the immune system further and help cure them of the virus. Pegylated interferon alpha-2a (Pegasys®) and pegylated interferon alpha-2b (Pegetron®) are the two types of interferon that may form part of the management of all genotypes of hepatitis C. Both pegylated interferon alpha-2a and pegylated interferon alpha-2b are given by subcutaneous injection once a week. After a teaching session by an experienced treatment provider, a patient can easily self-inject the medication at home. While pegylated interferon has been a mainstay of therapy for hepatitis C across genotypes in the past, the associated side-effect profile and limited efficacy in some individuals has driven ongoing research into superior therapies. Now, the first interferon-free regimens are widely available and represent the current standard of care for most individuals.

Ribavirin

Ribavirin is an anti-viral medication that has little effect by itself at curing the hepatitis C virus. However, its combination with pegylated interferon and/or direct acting antivirals may result in a treatment regimen that is more effective than either one alone. Ribavirin is in pill form, taken twice a day.

Direct Acting Antivirals (DAAs)

The hepatitis C virus replicates by using proteins to make copies of itself. While ribavirin and pegylated interferon are effective medications, they exert their anti-viral effects largely by indirect methods that do not specifically target the viral replication proteins.

Researchers have developed exciting new therapies to attack the hepatitis C virus by directly inhibiting proteins that are vital to the virus's ability to replicate. These direct acting antiviral (DAA) medications are now in wide use across hepatitis C genotypes. Many different DAAs with unique mechanisms of action are now available for use either in combination, with or without ribavirin, and in some cases with pegylated interferon as well.

Sofosbuvir (Sovaldi®): Sofosbuvir is an NS5B nucleotide polymerase inhibitor, taken orally as a single tablet, once daily. It is used in combination with ribavirin alone for treatment durations of 12 to 24 weeks (in genotypes 2 and 3), or with pegylated interferon and ribavirin for 12 weeks (in genotypes 1, 2, and 3).

Sofosbuvir/Ledipasvir (Harvoni®): Ledipasvir is an NS5A inhibitor, which has been co-formulated with sofosbuvir into an all-oral single-tablet regimen, called Harvoni®, taken once a day. This regimen when taken for 8 to 24 weeks is currently widely

used in Canada for genotype 1 disease with emerging data in other genotypes.

Ombitasvir/paritaprevir/ritonavir and dasabuvir (Holkira™ PAK): Holkira™ PAK is an all-oral combination of three DAAs plus ritonavir that is taken as 4 pills divided into twice daily dosing. The regimen includes a NS3 protease inhibitor, an NS5A inhibitor, and a non-nucleotide NS5B polymerase inhibitor. It is used with or without ribavirin for a treatment duration of 12 (most individuals) or 24 weeks depending on the individual patient. In Canada, it is approved and widely used for genotype 1 individuals only, although there are data in other genotypes.

Cure Rates

Sustained virologic response (SVR) refers to an inability to detect the hepatitis C virus in the blood 24 weeks after the completion of therapy. If this is achieved, a person is considered cured of the virus. It is important to note that cure does not protect against re-infection. Cure rates depend not only on the genotype of hepatitis C, but also on a person's previous treatment experience and other factors in his or her medical history. The following is therefore a guideline that provides a general idea of cure rates with current medications for the most common genotypes in Canada.

Genotype 1

The current standard of care therapy for genotype 1 hepatitis C is either Harvoni® or Holkira™ PAK. In certain circumstances, there may still be a role for pegylated interferon and ribavirin-based therapies. Current cure rates for the vast majority of genotype 1 individuals with either of these potent combination DAA therapies is >95%. Response rates, as well as the optimal treatment regimen and duration, still vary depending on the circumstances, so these are important conversations to have with your health care provider.

Genotypes 2 and 3

Appropriate current therapy for genotypes 2 and 3 hepatitis C may either be the combination of pegylated interferon and ribavirin used for 24 (up to 48) weeks; sofosbuvir plus ribavirin for 12 to 24 weeks; or sofosbuvir, ribavirin, and pegylated interferon for 12 weeks. While high cure rates >90% are expected for many individuals, depending on the regimen used and the specific clinical circumstances, these rates do vary and should be discussed in detail with your health care provider. Specifically, achieving high cure rates in individuals with genotype 3 hepatitis C with advanced fibrosis and prior treatment experience remains an unmet need and area of active research.

Side Effects of Therapy

One of the greatest concerns for people seeking treatment for hepatitis C is the side effect profile of the medications used. Widespread availability of interferon-free regimens for many individuals has significantly changed this, and the tolerability of these newer regimens, in general, is exceedingly good. While it is true that interferon-containing therapies may still carry significant side effects for the great majority of individuals, these are manageable and do not result in the need to discontinue treatment. While some individuals experience very mild or no side effects, and others experience very severe side effects, the majority will fall somewhere in the middle. A positive outlook and a good support system (friends, family, health care providers) can greatly improve a patient's ability to cope with and manage side effects during therapy. Common side effects of interferon-containing regimens include fatigue, fever, chills, muscle aches and pains, low red blood cell count (anemia), low white cell count (leukopenia), and rash. Other side effects may include irritability, depressed mood, and gastrointestinal symptoms. The side effect profile of interferon-free therapies is usually limited to mild fatigue, headache, and/or nausea for some individuals.

Other medications (both over-the-counter and prescription) may interact with hepatitis C medications, so patients should discuss any new medications with their health care providers.

Remaining active and in a positive frame of mind will help patients cope with their side effects and reach the end of therapy with the greatest chance of achieving cure.

Outlook

The future of hepatitis C lies in the education of health care providers and the public so that professionals can identify and offer treatment when possible to the many individuals with this curable condition. Experts are optimistic that research into new therapeutic options for hepatitis C and an ongoing interest in learning more about this condition over the coming years will result in the following:

- excellent cure rates for patients with all genotypes,
- very short therapy duration (4-6 weeks!),
- pan-genotypic therapies that are dosed independent of viral genotype,
- better access to medication for all,
- a vaccine for hepatitis C, and
- worldwide eradication of hepatitis C.

Find Out More

Ongoing research continues to reveal more about the symptoms, causes, cures, treatments, and preventative measures associated with GI and liver conditions. It would be our pleasure to send you a full information package on this topic. Please view our hepatitis C video at www.badgut.org.

NOTES:

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