INTRODUCTION

Hepatitis C

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV). The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, liver cancer or life-threatening esophageal and gastric varices ***(Ryan and Ray, 2004).***

HCV is spreads primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment and transfusions. An estimated 130–200 million people worldwide are infected with hepatitis C ***(Gravitz, 2011).***

The virus persists in the liver in about 85% of those infected. This persistent infection can be treated with medication: the standard therapy is a combination of peginterferon and ribavirin, with either boceprevir or telaprevir added in some cases. Hepatitis C is the leading cause of liver transplantation, though the virus usually recurs after

transplantation. Egypt is one of the countries with particularly high rates of infection (22%) ***(Wilkins et al., 2010).***

Chronic infection

About 80% of those exposed to the virus develop a chronic infection (***Davis GL, 2011)***. Hepatitis C after many years becomes the primary cause of cirrhosis and liver cancer ***(Ray and Thomas, 2009).*** About 10–30% of people develop cirrhosis over 30 years ***(Wilkins et al., 2010 and Davis GL, 2011).*** Those who develop cirrhosis have a 20-fold greater risk of hepatocellular carcinoma, a rate of 1–3% per year, ***(Wilkins et al., 2010 and Davis GL, 2011).*** Hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma worldwide liver cancer ***(Ray and Thomas, 2009).***

Liver cirrhosis may lead to portal hypertension, ascites, easy bruising or bleeding, varices, jaundice, and a syndrome of cognitive impairment known as hepatic encephalopathy. It is a common cause for requiring a liver transplant ***(Nicot, 2004).***

Treatment

HCV induces chronic infection in 50–80% of infected persons. Approximately 40-80% of these clear with treatment

(Torresi et al., 2011 and Ilyas and Vierling, 2011). In rare cases, infection can clear without treatment (***Davis GL, 2011).***

Medications

As of 2010, treatments consists of a combination of pegylated interferon alpha and the antiviral drug ribavirin for a period of 24 or 48 weeks, depending on HCV genotype (***Davis GL, 2011).*** When combined with ribavirin, pegylated interferon-alpha-2a may be superior to pegylated interferon-alpha-2b, though the evidence is not strong ***(Awad et al., 2010).*** Improved outcomes are seen in 50–60% of people (***Davis GL, 2011).*** Combining either boceprevir or telaprevir with ribavirin and peginterferon alfa improves antiviral response for hepatitis C genotype 1 ***(Foote et al., 2011); Smith et al., 2011 and Ghany et al., 2011).*** Adverse effects with treatment are common, with half of people getting flu like symptoms and a third experiencing emotional problems.[10] Treatment during the first six months is more effective than once hepatitis C has become chronic ***(Nicot, 2004).***

Interferon

Interferons (IFNs) are proteins made and released by host cells in response to the presence of pathogens such as viruses,

bacteria, parasites or tumor cells. They allow for communication between cells to trigger the protective defenses of the immune system that eradicate pathogens or tumors. IFNs belong to the large class of glycoproteins known as cytokines. Interferons are named after their ability to "interfere" with viral replication within host cells. IFNs have other functions: they activate immune cells, such as natural killer cells and macrophages; they increase recognition of infection or tumor cells by up-regulating antigen presentation to T lymphocytes; and they increase the ability of uninfected host cells to resist new infection by virus. Certain symptoms, such as aching muscles and fever, are related to the production of IFNs during infection..All interferons share several common effects; they are antiviral agents and can fight tumors. Some of those treated with interferon have a sustained virological response and can eliminate hepatitis virus. The most harmful strain—hepatitis C genotype I virus—can be treated with a 60-80% success rate with the current standard-of-care treatment of interferon-α, ribavirin and recently approved protease inhibitors such as Telaprevir (Incivek) or Boceprevir (Victrelis) ***(Ge et al., 2009)***.

Biopsies of patients given the treatment show reductions in liver damage and cirrhosis. Control of chronic hepatitis C by

IFN is associated with reduced hepatocellular carcinoma ***(Ishikawa, 2008)***.

Polyethylene glycol is added to make the interferon last longer in the body. Initially used for production of PEGylated interferon-alpha-2b (Pegintron), approval for PEGylated interferon-alpha-2a (Pegasys) followed in October 2002. These PEGylated drugs are injected once weekly, rather than administering three times per week, as is necessary for conventional interferon-alpha. When used with the antiviral drug ribavirin, PEGylated interferon is effective in treatment of hepatitis C; at least 75% people with hepatitis C genotypes 2 or 3 benefit from interferon treatment, although this is effective in less than 50% of people infected with genotype 1 (the more common form of hepatitis C virus in both the U.S. and Western Europe) ***(Jamall et al., 2008; NIH Consensus Statements, State-of-the-Science Statements, 2002 and Sharieff et al., 2002)***.

The most frequent adverse effects are flu-like symptoms: increased body temperature, feeling ill, fatigue, headache, muscle pain, convulsion, dizziness, hair thinning, and depression. Erythema, pain and hardness on the spot of injection are also frequently observed. IFN therapy causes

immunosuppression, in particular through neutropenia and can result in some infections manifesting in unusual ways ***(Bhatti and Berenson, 2007).***

Ribavirin

Ribavirin is a guanosine (ribonucleic) analog used to stop viral RNA synthesis and viral mRNA capping, thus, it is a nucleoside inhibitor ***(Carter and Saunders, 2007).*** Ribavirin is active against a number of DNA and RNA viruses. It is a member of the nucleoside antimetabolite drugs that interfere with duplication of viral genetic material. Ribavirin is active against influenzas, flaviviruses, and agents of many viral hemorrhagic fevers.In Europe and the U.S. the oral (capsule or tablet) form of ribavirin is used in the treatment of hepatitis C, in combination with pegylated interferon drugs ***(Torriani et al,. 2004).***

Mechanisms of action

Ribavirin's carboxamide group can make the native nucleoside drug resemble adenosine or guanosine, depending on its rotation. For this reason, when ribavirin is incorporated into RNA, as a base analog of either adenine or guanine, it pairs equally well with either uracil or cytosine, inducing mutations

in RNA-dependent replication in RNA viruses. Such hypermutation can be lethal to RNA viruses ***(Crotty et al., 2002)***.

Side effects

Ribavirin is not substantially incorporated into DNA, but does have a dose-dependent inhibiting effect on DNA synthesis, as well as having other effects on gene-expression. Possibly for these reasons, significant teratogenic effects have been noted in all non-primate animal species on which ribavirin has been tested. Ribavirin did not produce birth defects in baboons, but this should not be an indication that it is safe in humans. Therefore, two simultaneous forms of birth control are recommended during treatment of either partner and continued for six months after treatment. Women who are pregnant or planning to become pregnant are advised not to take ribavirin. Of special concern with regards to teratogenicity is ribavirin's long half-life in the body. Red blood cells (erythrocytes) concentrate the drug and are unable to excrete it, so this pool is not completely eliminated until all red cells have turned over, a process estimated to take as long as 6 months. Thus in theory, ribavirin might remain a reproductive hazard for as long as 6 months after a course of the drug has ended. Drug packaging

information materials in the U.S. now reflect this warning.Ribavirin should not be given with zidovudine because of the increased risk of anemia ***(Alvarez et al., 2006)***; concurrent use with didanosine should likewise be avoided because of an increased risk of mitochondrial toxicity ***(Bani-Sadr et al. 2005)***.

Prognosis

Responses to treatment vary by HCV C genotype, and is measured by sustained viral response. Sustained response is about 40-50% in people with HCV genotype 1 given 48 weeks of treatment ***(Houghton, 2009).*** Sustained response is seen in 70-80% of people with HCV genotypes 2 and 3 with 24 weeks of treatment ***(Houghton, 2009)***. Sustained response is about 65% in those with genotype 4 given 48 weeks of treatment. Successful treatment decreases the future risk of hepatocellular carcinoma by three quarters.