Hepatitis C Part I: Pathogenesis and Allopathic Therapeutics

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Abstract

Chronic hepatitis C infection is of greatly increasing concern. The incidence of detected infection is exploding worldwide and is estimated at 4 million cases in the United States. Hepatitis C is diagnosed and monitored with a series of antibody and polymerase chain reaction testing. Hepatitis C infection becomes chronic in 85% of those infected and may lead to slowly progressive damage of the liver. Over decades this damage can lead to cirrhosis, liver failure, and liver cancer. Many other chronic illnesses and auto-immune processes have been linked to hepatitis C infection. Allopathic treatments for this condition are somewhat effective but carry significant side effects, leaving a need for naturopathic medicine to step forward with effective natural therapies. (J of Naturopathic Med 2000;9:51-57)

Introduction

Chronic hepatitis C is being diagnosed in epidemic proportions, infecting an estimated four million Americans. The National Institutes of Health estimate 8,000-10,000 people in the U.S. die every year from hepatitis C-related liver disease and that without effective treatment this number is expected to triple in the next 10-20 years (1). Prior infections are now reaching the clinical stage in what is emerging as the next viral epidemic health crisis. Hepatitis C virus often exists insidiously in an infected individual for 10 to 20 years before symptoms appear and a diagnosis is made (14). By the time of diagnosis many of these individuals already have advanced liver destruction. Hepatitis C is the leading cause of advanced liver disease requiring liver transplantation in North America and Europe (1,5). The lack of effective conventional therapies for the disease compounds the situation and in many cases patients resign themselves to having a progressive chronic disease with little option but to wait and hope for a transplant when their liver ultimately fails.

This discussion of hepatitis C will be in three parts. This first segment will discuss the current medical understanding of hepatitis C, its diagnosis, pathogenesis, potential complications and current allopathic treatment options. Part II will discuss treatment of hepatitis C from a naturopathic and Chinese medicine perspective and Part III will present hepatitis C clinical case studies.

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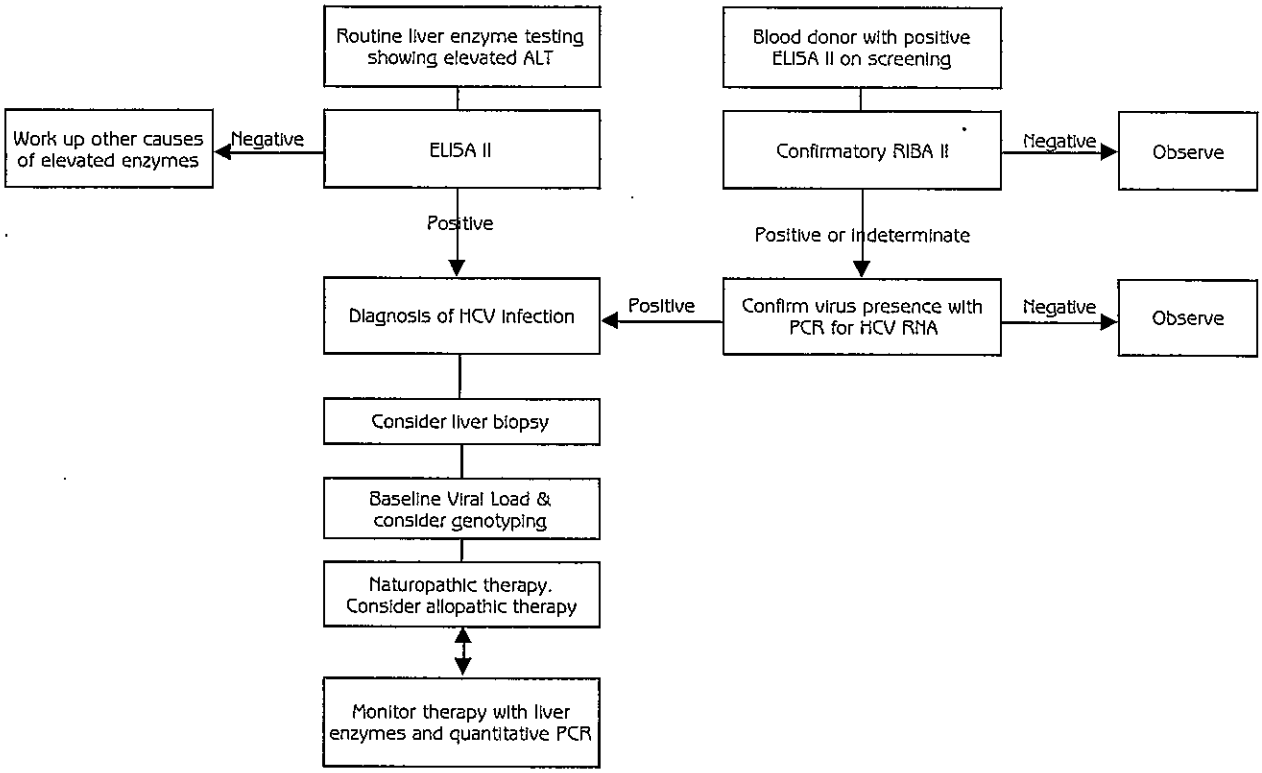
The Virus and Testing Methods

The hepatitis C virus (HCV) eluded researchers until 1989 when it was finally isolated through a process of viral cloning. HCV is a single-stranded, enveloped, ribonucleic acid (RNA) virus of the Flavivirdae family (3). HCV has an extremely high rate of genomic variability and mutation that allows it to evade the body's immune system. This evasiveness results in a very high rate of chronic infection and frustrates researchers in their attempts to develop effective treatments and a vaccine (2,3).

Three generations of enzyme-linked immunosorbent assay (ELISA) and recombinant immunoblot assay (RIBA) antibody testing have been developed and evolved to a greater than 95% sensitivity for HCV antibodies (4). The specificity of the ELISA for HCV is not as high as the sensitivity, resulting in a significant incidence of false positives. A positive ELISA after screening, therefore, usually requires confirmation of the HCV infection with either a RIBA or polymerase chain reaction test. A positive ELISA can be considered sufficient for diagnosis of HCV when in combination with clinical signs of liver disease or elevated aminotransferase levels (4).

FIGURE 1. PROPOSED ALGORITHM FOR EVALUATION OF SUSPECTED CHRONIC HEPATITIS C VIRUS INFECTION



The most sensitive test for HCV is the polymerase chain reaction (PCR) for determining the direct presence of the viral RNA. The quantitative PCR measures the viral concentration and the qualitative PCR detects specific genotype information for HCV. There are six known genotypes and over 80 subtypes of HCV (5). Knowing the particular genotype of the virus in an individual may affect treatment decisions and is helpful as a prognostic or research tool. Genotype I, which includes types 1a and 1b, has an increased risk for progression to cirrhosis and cancer, as well as being more resistant to conventional treatment. Type Ib confers a worse prognosis than type Ia (6,7). In the U.S., approximately 70% of HCV infections are genotype I (33).

Despite the higher sensitivity of the PCR, screening for hepatitis C infection is done with the less expensive and readily available ELISA and RIBA antibody tests (see Figure 1) (1,4,5). HCV PCR is useful diagnostically in low-risk blood donors with positive HCV antibodies but normal aminotransferase levels, in differentiating chronic HCV from autoimmune hepatitis and in patients refusing liver biopsy before consideration of allopathic therapy (5). Quantitative PCR testing for viral load is regularly used to monitor response to anti-viral therapy. This test, however, is notorious for its wide variability of viral level results between laboratories.

Liver biopsy is the gold standard for determining the extent of liver damage as a result of chronic hepatitis. Biopsies are generally performed in patients prior to interferon treatment to rule out hepatic cirrhosis. Patients with cirrhosis are not considered good candidates for interferon due to poor response rates and the potential risk of decompensation (ascites, jaundice, varices, and encephalopathy) (5,8).

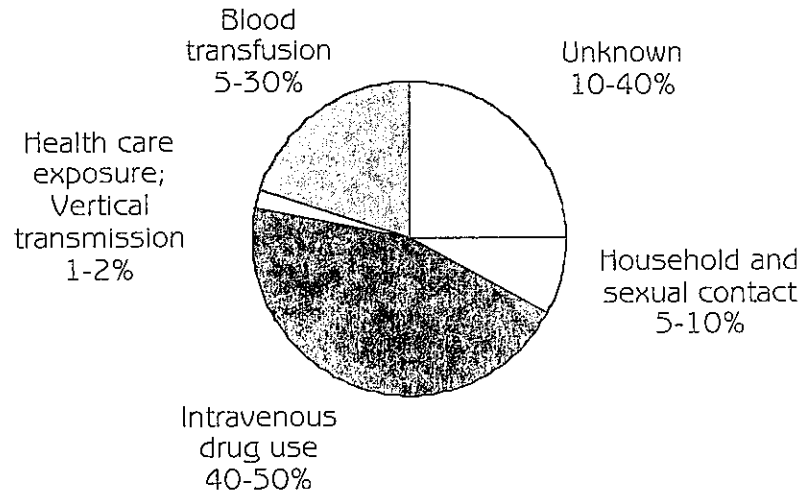
ROUTES OF TRANSMISSION

Prior to 1990 when blood banks in the United States began screening for HCV, millions of people were unknowingly exposed to the virus through hospital blood transfusions. Other major routes of transmission include intravenous drug use, hemodialysis, tattooing and piercing. HCV is much less likely to be transmitted through sexual contact than its counterpart hepatitis B virus (HBV), though this is still a viable route of transmission and is estimated to be the route of infection in 5-10% of hepatitis C cases (1,9). There is evidence of transmission of HCV through the nasal mucosa of cocaine users sharing straws and this may prove to be a significant transmission route (10). Interestingly, up to 40% of hepatitis C patients deny any high-risk parenteral exposures, possibly signifying that other routes of transmission have yet to be fully understood (see Figure 2) (5,10).

PREVALENCE

It is estimated that the prevalence of the hepatitis C virus in the general population of the United States is between 1.4 and 1.8% which corresponds to 3.5 to 4 million infected individuals (1,11,12). HCV infection in the U.S. is most prevalent in persons 30 to 49 years old (3-4%) particularly in the black population (3.2%), Mexican-American population (2.1%), and less so in the white population (1.5%) (1,12). The annual incidence of newly acquired hepatitis C infections in the U.S. has fallen from 180,000 in the mid 1980s to an estimated 28,000 new infections in 1995 (12). Although screening of the blood banks has certainly helped, most of the dramatic decline appears to correlate with a decrease in acute cases

FIGURE 2. SUSPECTED ROUTES OF TRANSMISSION FOR CHRONIC HEPATITIS C INFECTION



associated with IV drug use (12). The reason for this is not known but it is possible that increased awareness of HIV infection indirectly impacted the incidence of new cases of HCV infection.

NATURAL HISTORY

It is estimated that about 21% of all cases of acute viral hepatitis are a result of hepatitis C infection. Unlike hepatitis A and B, it is uncommon for HCV infection to begin with typical viral hepatitis symptoms. The illness most commonly starts with flu-like symptoms that, for the vast majority, go undiagnosed as HCV infection until many years later. In 80% or more of instances, persons with chronic HCV infection do not recall ever having had an illness resembling acute hepatitis (13).

A very high 85% (up from estimates of 50% a few years ago) of HCV infections will develop into the chronic hepatitis state in the infected individual (1). In contrast, hepatitis B patients have only a 5-10% risk of developing a chronic state of infection. Chronic HCV infection rarely resolve spontaneously. Chronic patients have at least a 20 to 30% risk of progression to liver cirrhosis and about 20% of those progress to liver cancer (13,14).

The natural history of the disease caused by HCV has been very difficult to define because of the mild versions of the early disease that are often missed, the slow progression, and the large number of HCV positive individuals who are asymptomatic until advanced stages of the disease. Several studies have been conducted to try and quantify the risk of progression from HCV infection to chronic liver disease but these studies have been limited in their ability to capture the full natural history (14). Most of these studies have not exceeded 10-15 years in duration which is insufficient to cover the full course of the disease. In two retrospective/prospective (non-concurrent prospective) studies, one from Japan and one from the U.S., progression from apparent acute infection to chronic hepatitis, then to cirrhosis, and finally to hepatocellular carcinoma (HCC) was estimated to average 10 years, 20 years, and 30 years respectively (39,40). Some individuals developed liver cancer 40-50 years after the presumed initial infection. In five prospective studies, clinical symptoms have been noted in about 10% of cases, histologic cirrhosis in 15% to 20%, and HCC identified in 0.7% to 1.3%. Mortality ranged from 1.6% to 6.0% (34-38).

Certain factors are known to accelerate the progression of chronic liver destruction in HCV-infected patients. The genotype 1b of HCV has an increased likelihood of rapid progression to cirrhosis and liver cancer (6).High levels of iron in the liver, possibly as a result of hemochromatosis, also increase the rate of progression of liver disease (15). Alcohol intake should be avoided by HCV infected individuals as it accelerates the progression of HCV to chronic liver disease and decreases overall survival (16).

One of the most detrimental factors to a patient with HCV is co-infection with other viruses, particularly human immunodeficiency virus (HIV) and hepatitis A virus (HAV). Co-infection with HIV may accelerate the average rate of progression to cirrhosis from 20 years to 6 years (17). Hepatitis A rarely causes fatal consequences but it has recently been found that superinfection of HAV in chronic HCV carriers can dramatically increase the incidence of fatal fulminant hepatitis (18). The danger of such a course of acute hepatic failure has prompted the NIH to advise vaccination against hepatitis A for all individuals with chronic HCV infection (1).

CHRONIC HEPATITIS

Chronic hepatitis is defined as a hepatitis lasting longer than six months (19). Chronic hepatitis can further be classified as either chronic persistent or chronic active. Chronic persistent hepatitis is a relatively benign disorder that follows typical acute hepatitis, and has high amino transferase values with no signs of clinical liver disease (19).

Chronic active hepatitis, on the other hand, is a serious disorder that can often lead to liver cirrhosis and/or liver failure. Hepatitis C infection is the major cause of chronic active hepatitis (12). The pathogenesis is not completely understood but an abnormal or excessive immune response to the virus seems likely. Injury to the liver appears to be due to an immune-mediated host reaction to the infection rather than to direct cytotoxic activity of the virus (19). True autoimmune response has not been shown—auto-antibodies directed against liver cells have not been found. Ian Wanless MD, professor of pathology and director of the Canadian Liver Pathology Reference Center, proposed in his presentation to the Liver Disease & Hepatitis Conference in June 1997 that the mechanism of progression to cirrhosis involves damage and obstruction to the portal and hepatic veins due to phlebitis and thrombosis (20). The phlebitis and thrombosis proposed by Dr. Wanless may be the result of virally related immune complex agglutination in the vasculature of the liver.

Signs and Symptoms of Chronic Liver Disease

Symptoms of chronic active hepatitis vary and are often non-specific including malaise, anorexia and fatigue as the most common. Often the patient will present with upper right quadrant discomfort and possibly low-grade fever. With advancing liver disease serious clinical features that may appear include jaundice, cholestasis, hepato- and splenomegaly, portal hypertension, ascites, and hepatic encephalopathy.

Jaundice is a yellowing of the skin, sclerae, and other tissues due to an excess of circulating bilirubin. Bilirubin is formed primarily from the breakdown of red blood cells and then conjugated by the liver into a water-soluble form that can be excreted via feces, bile, and to a small degree in the urine. In hepatic disease the liver's ability to take in bilirubin, conjugate it and then release the soluble product can all become impaired leading to an increase in circulating bilirubin. Jaundice is usually detectable when the serum bilirubin reaches 2-2.5 mg/dL and is best seen by examining the sclerae in natural light.

Cholestasis refers to an impairment of bile flow. In hepatitis, advanced liver cirrhosis, and carcinoma, the bile can be physically or biochemically backed up into the liver. The most common signs and symptoms of cholestasis are jaundice, dark urine, pale stools, and generalized pruritus .

Hepatomegaly is enlargement of the liver as a result of either primary or secondary liver disease. Lack of hepatomegaly, however, does not rule out serious liver disease. The normal width of the liver along the right midclavicular line is between 6-12 cm. The lower border of the liver is normally palpable just under the right costal margin with a smooth, rubbery, and sharp edge. A cirrhotic liver may feel firm, blunt and irregular with possible nodules. Excessive liver tenderness may or may not be associated with hepatomegaly.

Portal hypertension refers to the increase in pressure experienced in the main blood vessel of the liver, the portal vein. The portal vein is responsible for carrying all blood from the GI tract, spleen, pancreas, and gallbladder through the liver and back to the heart. Hardening of the liver tissue is the most common cause of increased resistance to blood flow within the liver leading to portal hypertension. The complications of portal hypertension are quite serious. As back pressure in the venous system builds, extra blood vessels may form to handle the increase in pressure, most commonly in the esophagus (esophageal varices) and abdomen (caput medusae). The formation of new vessels and the dilation of old vessels greatly increases the risk of bleeding and life threatening hemorrhage.

Ascites refers to free fluid in the peritoneal cavity. It is often a result of chronic liver disease but is not seen in acute liver conditions. Cirrhosis is again the major cause of this sign of liver disease due to an increase in portal venous pressure, change in electrolyte balance, and diminished protein synthesis by the liver. Shifting dullness on percussion of the abdomen as the fluid moves is the major clinical finding of this condition. Ascites is not specific to liver disease and may be a consequence of other conditions including heart disease, nephrotic syndrome, hypothyroidism, renal failure, and others.

Hepatic encephalopathy, also called portal-systemic encephalopathy, or hepatic coma, is a toxicity of the brain as a result of the liver losing its ability to properly metabolize blood products. The properly functioning liver detoxifies and metabolizes digestive products brought from the gut via the portal vein. In advanced liver disease these digestive by-products are not fully metabolized and can lead to cerebral inflammation. It is speculated that the ammonia created in protein digestion is a major contributor to the cerebral toxicity. Hepatic encephalopathy initially manifests as personality changes progressing to impaired consciousness with sluggishness, confusion, stupor, asterixis, and eventually coma. The condition is often reversible by removing the toxic by-products and limiting protein in the diet.

Other symptoms that commonly appear with liver disease include anorexia, fatigue, and weakness due to hepatocellular dysfunction. Skin changes may include spider nevi, palmar erythema, and Dupuytren's contractures (fibrous proliferation resulting in painless thickening and contracture of the palmer fascia). Endocrine imbalances happen commonly in patients with liver cirrhosis including glucose intolerance, hyperinsulinism, insulin resistance, and hyperglucagonemia. Sex hormones may also be affected resulting in amenorrhea and decreased fertility in women with chronic liver disease. Males with cirrhosis commonly experience testicular atrophy, impotence, decreased spermatogenesis, and gynecomastia. Blood disturbances are also common, often manifesting as anemia and coagulation problems due to impaired hepatic synthesis of clotting factors. Electrolyte balance and proper renal function may be disturbed in liver disease and should be suspected in cases with ascites. Hypokalemia, due to excessive urinary loss of potassium, and hyponatremia are common in advanced cases. Circulatory problems can lead to decreased kidney function, increased cardiac output, tachycardia, and clubbing of the fingers.

Extrahepatic Manifestations of Hepatitis C

Hepatitis C infection has been linked to a number of immunological markers and extrahepatic conditions (Table 1). Conditions that are strongly associated with HCV include: essential mixed cryoglobulinemia (EMC), membranoproliferative glomerulonephritis (MPGN), and porphyria cutanea tarda (PCT) (11). Other conditions that have been associated with HCV infection are B-cell non-Hodgkin lymphoma (B-cell NHL) (22), Mooren corneal ulcers(11), autoimmune thyroiditis (23), autoimmune thrombocytopenia and purpura (24), diabetes mellitus (25), Sjögren's syndrome (23), lichen planus (23), pulmonary fibrosis (11), fibromyalgia (26), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) (23), and polyarteritis nodosa (23).

Essential mixed cryoglobulinemia (EMC) is the most closely associated extrahepatic complication of HCV. It is a disorder that involves the deposition of circulating immune complexes in small and medium sized blood vessels. The globulins formed by the antigen-antibody complex precipitate with cold and obstruct micro-vasculature. The resulting clinical manifestations include: purpura, arthralgia, Raynaud's syndrome, peripheral neuropathy, systemic vasculitis, and glomerulonephritis. HCV-related membranoproliferative glomerulonephritis (MPGN) is believed to be a result of depositing globulins in the

TABLE 1. STRENGTH OF VARIOUS ASSOCIATIONS WITH CHRONIC HEPATITIS C INFECTION

Association
Strong association
- Essential mixed cryoglobulinemia
- Porphyria cutanea tarda
- Membranoproliferative glomerulonephritis

Suggested association
- Mooren corneal ulcers
- Autoimmune (Hashimoto's) thyroiditis
- B-cell non-Hodgkin lymphoma
- Fibromyalgia
- Autoimmune thrombocytopenia
- Diabetes

Weak association
- Sjögren's syndrome
- Lichen planus
- Idiopathic pulmonary fibrosis
- Rheumatoid arthritis
- Systemic lupus erythematosis
- Polyarteritis nodosa

TABLE 2. SYSTEMIC DISORDERS RELATED TO HCV INFECTION (27)

Disorder	Patients n	Anti-HCV %	HCV RNA %
EMC	110	91	86
EMC plus hepatitis	77	96	91
EMC plus MPGN	31	100	100
EMC and B-cell NHL	14	100	100
Chronic hepatitis C and B-cell NHL	14	100	100
Idiopathic B-cell NHL	50	30	32
Chronic hepatitis C and lung fibrosis	5	100	100
Porphyria cutanea tarda	23	91	77
Autoimmune hepatitis type 1	30	80	77
Immunologic diseases (SLE, RA Sjögren's syndrome, and systemic sclerosis)	110	6	5

EMC = Essential mixed cryoglobulinemia,
MPGN = Membranoproliferative glomerulonephritis
NHL = non-Hodgkin's lymphoma

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basement membrane of the glomerular apparatus. Other possible mechanisms include: virally-induced local immune complex formation, induced autoantibody reaction with local tissue, and/or direct virus reaction with extrahepatic tissue. The connection between EMC and the other complications of HCV is strongly implicated but not yet fully understood. Interferon is effective in treating EMC and MPGN in patients with hepatitis C, supporting HCV as an etiology of these conditions (41). Many chronic HCV patients also have an elevation of rheumatoid factor and other autoimmune markers that may lead to a higher incidence of certain autoimmune diseases (23). In a study conducted by Ferri and colleagues an incidence as high as 96% of patients with EMC were positive for HCV antibodies (22). This study also found that 30% of patients with non-Hodgkin's lymphoma were also positive for HCV antibodies (see Table 2) (27).

CONVENTIONAL TREATMENT

The first federally-approved initial therapy for chronic hepatitis C infection consists of interferon alpha. Interferons bind to specific receptors on the cell membrane, causing the release of enzymes that "interfere" with viral replication, uncoating, assembly, and cell entry. Interferons also directly increase natural killer cell activity and enhance maturation of cytotoxic T lymphocytes (28). The exact mechanism of action of alpha interferon in hepatitis C, however, is not fully understood (29).

Treatment usually consists of alpha interferon 2b at 3 million units subcutaneously three times a week for 24 to 48 weeks. Normalization of ALT occurs in about 40-45% of patients, and clearance of the HCV in about 30% of patients after 48 weeks of therapy (30). Relapse rate, however, is very high. In follow-up six months after the initial course of therapy, approximately 20% of patients sustain normalization of liver enzymes and about 8% remain clear of the virus (30). Recent studies have attempted to increase the sustained effectiveness of interferon by prolonged treatment time, higher doses, and combination therapy (30,32,33). The direct cost of interferon for a 6 month trial exceeds $2,100 (42). Kim, et al. demonstrated that the cost of interferon therapy per quality adjusted life year (QALY) varied greatly based on the age of the patient. They found that for a 12 month course of interferon therapy for hepatitis C the cost per QALY for age groups 30-, 40-, 50-, and 60- was $1,800, $3,700, $6,900, and $12,800 respectively (43). The study concluded that interferon therapy was cost effective in all those under 60 years old.

Another important issue with interferon therapy is the high incidence of unpleasant side effects. Very common side effects include malaise, headaches, musculoskeletal pain, skin rash, alopecia, anorexia, nausea, sleep disturbances, irritability, hearing loss, visual changes and depression (31). The immune-modulating effects of interferon can also induce various autoimmune side effects. The most common is autoimmune thyroiditis with either hypothyroidism or hyperthyroidism; autoimmune hepatitis, diabetes, thrombocytopenia, psoriasis, systemic lupus erythematosis, and primary biliary cirrhosis are also reported (31). Other serious side effects that are more rare include renal disorders, cardiomyopathy, and pneumonitis (31). Isolated cases of interferon therapy-related fatalities have been reported (31). Side effects require a reduction in interferon dosage in 10-40% of patients and discontinuation in 5-

10% (1). Contraindications to treatment with interferon include a history of depressive illness, decompensated cirrhosis, coronary artery disease, pregnancy, cytopenia, active alcohol or illicit drug use, hyperthyroidism, renal transplantation, or autoimmune disease (1, 31).

In June 1998 ribavirin was approved by the Food and Drug Administration to treat chronic hepatitis C in patients that had relapsed after initial interferon alfa therapy. Ribavirin is a synthetic nucleoside analogue with anti-viral action that has been effective in lowering liver enzymes in chronic hepatitis C sufferers but when administered alone has no effect on serum HCV RNA levels (32). Ribavirin is administered orally at 1000-1200 mg daily in combination with subcutaneous injections of interferon.

Studies have shown that ribavirin, when used in combination with interferon, increases the likelihood of a sustained positive response against the virus (32,33). Virologic markers show an increase to 30-38% of patients sustaining a negative HCV presence in the serum with the combination approach, including carriers of genotype 1 that previously had poor results with interferon treatment (33). Genotypes other than 1 have shown response rates as high as 70% with combination therapy. Unfortunately, there also appears to be an increase in incidence of many of the interferon's side effects as well as a new risk of a reversible hemolytic anemia known to be associated with ribavirin (33). Ribavirin is associated with a significant risk of abnormal fetal development requiring initial and monthly pregnancy tests for women of childbearing age choosing the therapy. Combination therapy for hepatitis C, therefore, has increased the effectiveness of conventional treatment by roughly double but requires careful monitoring of hemoglobin levels, and has a higher incidence of side effects requiring more frequent drug reduction and discontinuation than with interferon treatment on its own (33).

Conclusion

Chronic hepatitis C is a rapidly growing health concern in the United States and the rest of the world. With as many as four million infected individuals in the U.S. and the incidence of complications on the rise this disease is challenging allopathic and naturopathic doctors alike. It is important for naturopathic doctors to understand the pathology and testing of the disease and the seriousness of the potential complications. It is also important to be able to discuss with our patients the pros and cons of allopathic therapy. As seen, a large majority of hepatitis C sufferers are not successfully treated by allopathic means, and many are looking for alternative options. Naturopathic doctors and herbalists are being sought out by an increasing number of these patients. Naturopathic medicine's emphasis on immune support, detoxification and restoration of normal tissue function is perfectly positioned to face this challenge. Part II will present effective treatment options from the fields of naturopathic and Chinese medicine.

Next Issue: Naturopathic Treatment of Hepatitis C

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Biography

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