Preventive Approaches in Chronic Liver Diseases, Part I

by Mohammad R. Taheri, Thomas R. Riley III

Hepatitis C virus is the leading cause of chronic liver disease (CLD) worldwide and non-alcoholic fatty liver disease in the western world. Preventive measures can significantly reduce the progression of liver disease to cirrhosis and liver cancer. This review will discuss preventive measures with proven benefits. Alcohol abstinence is recommended to patients with CLD. Immunization for hepatitis A and B should be provided to patients with CLD. Medications and herbals should be used carefully in these patients to avoid potential hepatotoxicity. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided and acetaminophen is safe at doses of less than 2 grams daily. Weight control and regular exercise is recommended in patients with CLD. Part II and III will address preventive approaches in those with compensated hepatic cirrhosis and decompensated cirrhosis respectively.

INTRODUCTION

Chronic liver disease (CLD) is the 12th leading cause of mortality in the United States (US). Hepatitis C virus (HCV) is the leading cause of CLD with an estimated worldwide prevalence of about 2.2% (1,2). Combination regimens of pegylated interferon and ribavirin have the ability to provide a sustained virological response in up to 40%–50% of the patients with chronic HCV leaving a large number of patients with chronic infection (3).

Hepatitis B virus (HBV) is another major cause of CLD which can lead to liver cirrhosis and hepatocellular carcinoma. In the US, an estimated 1.25 million individuals are HBV carriers and 73,000 new cases of HBV infection are reported annually (4). Immigrants from China to the US have a rate of infection 35 times higher than in the U.S. population, with liver cancer rates about 10 times higher than Caucasians. Several anti-HBV therapies including interferon alpha, lamivudine, adefovir, entecavir and recently pegylated IFN and talbivudine have been approved for the management of chronic hepatitis B infection with variable results (4).

Other categories of CLD include toxin related diseases (like alcohol), autoimmune diseases (including primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis), hereditary diseases (e.g., α-1 antitrypsin, hemochromatosis, Wilson’s disease), non-alcoholic fatty liver diseases and cryptogenic liver diseases. The progression of these liver diseases is often slow, taking up to 20–50 years to develop liver cirrhosis or decompensation.

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The main objective of this article is to focus on the preventive measures that are scientifically proven to help in the management of patients with CLD and delay the onset of liver related complications.

LIVER DISEASE AND ALCOHOL CONSUMPTION
Alcohol related liver disease involves a variety of entities like fatty infiltration of the liver to more severe forms such as alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma. The daily consumption of 48 grams of alcohol, which accounts for about four alcoholic drinks, increases the risk of liver cirrhosis as well as death from other causes (5–7).

Alcohol is not only a major cause of liver disease but also has a negative effect on other causes of CLD. Alcohol abuse coexists frequently in patients infected with HCV. This has a detrimental effect on the liver disease. In a study done by Corrao, et al, the effect of alcohol in patients with HCV infection was shown to not only be additive but synergistic and even moderate use of alcohol could accelerate the progression to cirrhosis (8). Monto, et al related the amount of alcohol intake and its effect on HCV infection. In this study, patients with HCV had increases in both the mean liver fibrosis and the odds ratio for fibrosis even among patients with less than 50 g/day of alcohol consumption. Monto concluded that light intake of alcohol exerts less of an effect on fibrosis than heavy intake and indeed may have minimal or no effect (9).

The main question is the quantity of alcohol that it is considered to be safe in patient with CLD. What is clearly accepted is that consumption of four alcoholic drinks daily has the potential for devastating effects on the liver. The literature addressing light alcohol intake in CLD is conflicting (10). If the patient does not have a history of alcohol or other drug addiction, some experts tolerate the use of one drink per day but others suggest that even this small amount of alcohol could exacerbate the liver injuries. Abstinence is the safest recommendation given this uncertainty in CLD to prevent an accelerated course to cirrhosis.

Abstinence can be difficult due to the strong additive potential of alcohol. Treatment approaches for these patients are a combination of psychosocial and pharmacological interventions (11). The most used pharmacotherapies are naltrexone and acamprosate which have been shown to improve outcome in rehabilitation of alcohol-dependent patients (12). Naltrexone reduces the risk of relapse to heavy drinking and the frequency of drinking but does not enhance abstinence (11). Acamprosate is believed to maintain abstinence by blocking the craving (12). Selective serotonin reuptake inhibitors (SSRI) have an indirect effect on drinking behavior of patients by treating co-morbid conditions like depression with a positive effect on drinking habits (12).

In a study done by Cordoba, et al, brief counseling of 15 minutes duration by physicians compared to simple advice had a significant decrease in frequency of excessive drinking after 12 months of follow-up (67% versus 44%) (13). This counseling consisted mainly of alcohol quantification, information on safe limits, advice, drinking limits agreement, self-informative booklet with drinking diary record and unscheduled reinforcement visits. The simple advice consisted of only the first three points mentioned above (13–15). Therefore, a brief intervention by a primary care physician could have a tremendous effect in the patients drinking habits. Inpatient rehabilitation has shown favorable results with about a 40% success rate of abstinence after four years (16). Outpatient rehabilitation programs have become popular in recent years. Bottlender, et al showed abstinence rates up to 43% in patients attending (17). These studies suggest that outpatient rehabilitation could be as effective as inpatient. Individual counseling and support groups like Alcoholics Anonymous and community/religious groups have shown to be effective in achieving and maintaining abstinence (5).

LIVER DISEASE AND “HEPATOTOXIC” MEDICATIONS
The total number of medications that are toxic to the liver is unknown, but about 1000 drugs are reported to be hepatotoxic (18,19). Most medications are metabolized and chemically altered in the liver. The liver is involved in the process of clearance, detoxification, excretion and activation of drugs. An injured liver is impaired and thus unable to satisfy these functions. Dosages of medication that are “safe” in patients with...
normal liver function may not be safe in patients with CLD. This impairment is directly related to the degree of damage of the liver. Patients with CLD may be at increased risk for idiosyncratic drug reactions, and less able to handle toxicity when it occurs. Drug induced liver injury (DILI) is classified as hepatocellular, cholestatic or mixed (20). Nevertheless, not all jaundice that develops in a patient taking a potentially hepatotoxic drug is caused by the drug. A thorough search for other causes should be carried out first, since DILI is a diagnosis of exclusion (21). Studies of patients with only jaundice from severe acute hepatocellular DILI demonstrate a short-term mortality as high as 10%, but those with fulminant hepatitis have only a 20% likelihood of survival without liver transplantation (22). The mechanism responsible for hepatocellular DILI is largely unknown but may be a result of host metabolic idiosyncrasy (23). Implicated, but yet uncertain, mechanisms include mitochondrial toxicity, oxidative stress, and hepatic steatosis, necrosis or apoptosis (23).

Several classes of drugs are known to have some degree of hepatotoxicity. These are anabolic steroids, anticonvulsants, antidepressants, anti-tuberculous agents, lipid lowering agents, muscle relaxants, non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 (COX-2) inhibitors, oral hypoglycemic agents, and psychotropics. A list of selected hepatotoxic medications is provided (Table 1). Other drugs like antibiotics, anti-fungals, anti-virals and anti-protozoal have more potential for idiosyncratic drug reactions.

All medications should be evaluated for possible hepatotoxicity in patients with CLD. These drugs should be avoided in these patients and a non-hepatotoxic alternative should be selected as a first choice. If no alternative is available, then the drug may be provided to the patient with extreme caution and under close supervision. The patient needs to be aware of the symptoms of liver injury (like nausea and vomiting, jaundice, abdominal pain mainly in right upper quadrant, pruritus, anorexia and fatigue) and should report such symptoms immediately to their physician.

The need for periodic liver test monitoring when a normal patient is started on a possible hepatotoxic drug is debated (18). This dilemma does not apply to patients with CLD. Those with CLD need to have a baseline liver injury panel done before starting the new medication with repeat of the tests every two weeks for the first month, monthly for three months and then every three months. The mentioned panel includes transaminases, total bilirubin and alkaline phosphatase. The medication should be discontinued if there is an increase more than three times the baseline levels, or if a symptom of acute liver injury occurs.

Patients should be advised on the use of over-the-counter pain and arthritis medications. The hepatotoxicity of NSAIDs is unpredictable. Several reports have associated NSAIDs to fulminant liver failure (24). A case series by Riley, et al described the use of ibuprofen associated with more than a 20-fold increase in liver function test values in three patients with chronic hepatitis C infection (25). Due to this unpredictability, NSAIDs should be avoided in patients with CLD.

Acetaminophen is the other over-the-counter medication that is widely used. The hepatotoxicity of acetaminophen is well known and studied. It has a dose dependant toxicity on the liver. The simultaneous
use of alcohol intake (or starvation) can increase the hepatotoxicity of acetaminophen (26), but the 2 gram dose provides a safe buffer zone without reported cases of injury at this level of ingestion. Recently, Watkins, et al showed that the use of acetaminophen in doses up to 4 grams daily could produce an elevation of liver function tests even in subjects with no liver diseases, further suggesting a dose reduction for those with chronic liver disease is appropriate (27). Acetaminophen is therefore the pain medication of choice at doses of less than or equal to 2 grams a day in CLD.

LIVER DISEASE AND SUPPLEMENTS/HERBS/VITAMINS

The use of dietary supplements, like vitamins and herbal remedies, has been increasing during the past decade in the US. This industry has gone from 1.8 billion (1990) to 5.1 billion dollars a year (1997) (28,29). Herbal products are not regulated by the Food and Drug Administration (FDA); therefore, their safety is questioned by the medical community (29). The public considers herbal remedies and vitamins to be safe, in contrast to conventional drugs. One of the reasons for this mis-guided belief is that these products do not require prescriptions therefore “should be safe” (30). Many of these products have a direct effect on the liver. As their usage has increased substantially in recent years, the hepatotoxicity of these compounds has become a focus of attention. The diagnosis of hepatotoxicity, resultant from alternative products, is a challenging task for physicians. The diagnosis is often delayed because of lack of disclosure of herbal use. Also, the exact composition of herbal remedies is not fully available as there are discrepancies between the labels and actual contents (30). Obtaining a thorough medical history with focus on alternative medication is vital for a primary care physician as the public does not consider these products to be medications. A list of most hepatotoxic herbal products with their application and clinical presentation is provided (Table 2).

Not all herbal products are hepatotoxic. Silybum marianum, milk thistle, might even be beneficial. Milk thistle use has not been associated with hepatotoxicity and there is weak evidence of hepatocyte plasma membrane protective effect. Given the lack of toxicity and possible efficacy, milk thistle is considered safe in patients with CLD (31).

Vitamins may also have toxic effects in the setting of liver disease. Vitamin A is the supplement known with a well reported hepatotoxicity. Several reports of hepatotoxicity with doses as high as 100,000 international units (IU) daily have been reported; although, rare cases of liver damage with even lower doses have been reported (32). Nollevaux, et al showed that the Hypervitaminosis A produces perisinusoidal fibrosis of the liver with correlation between the severity of the fibrosis and the daily dose of Vitamin A intake suggesting the existence of a dose-effect relationship (33). It is recommended that patients with chronic liver disease do not consume more than 10,000 IU per day of vitamin A (32). Most multivitamin preparations (MVI) contain less than 4,000 IU per pill; therefore, safe for daily use.

Chronic injury to the liver leads to parenchymal accumulation of iron. The mechanism behind this is not well understood. This secondary hemosiderosis should be differentiated with respect to primary hemochromatosis which is related to a genetic defect leading to iron accumulation in the liver parenchyma. About 30% of patient with chronic liver disease have high serum iron levels and up to 10% have excessive iron on their liver biopsy (34,35). Overt iron overload in the liver has the potential of initiating the oxidative-stress responses; thus, potentiating ongoing inflammatory processes. In the presence of CLD, less iron is required to initiate oxidative stress injury (36). Several studies have shown that increased liver iron concentration is predictive of failure to respond to interferon treatment in patients with chronic hepatitis C (37,38). Furutani, et al showed that iron overload increases the risk of hepatocellular carcinoma development in transgenic mice expressing the HCV infection (39). There has been no scientific evidence suggesting that dietary iron is harmful to patients with CLD but iron supplementation (part of many MVI preparations) should be avoided unless medically indicated.

LIVER DISEASE AND IMMUNIZATION

A chronically diseased liver is “fragile” to new injuries. A new injury to an already damaged liver could have detrimental effects. A viral infection like
hepatitis A, which is usually well tolerated in a normal host, can produce devastating effects in patients with CLD and lead to acute liver failure (40). Several studies have shown the dangers of hepatic “super-infection” (41,42). Liaw, et al concluded that acute HCV super-infection in patients with chronic HBV shows a similar type of presentation as infection with hepatitis D virus (HDV); also, the CLD shows more rapid progression to cirrhosis and liver cancer (41). Vento, et al showed, in a prospective study done in Italy that the mortality rate among patients with chronic hepatitis C and HAV super-infection could be as high as 35% (42).

### Table 2

<table>
<thead>
<tr>
<th>Herbal product</th>
<th>Reason for usage</th>
<th>Clinical manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actaea racemosa (Black Cohosh)</td>
<td>Menopausal symptoms</td>
<td>Severe hepatitis, fulminant hepatic failure.</td>
</tr>
<tr>
<td>Callicepis Laureola</td>
<td>Various such as stomach complaints, cough, and impotence.</td>
<td>Acute hepatic failure</td>
</tr>
<tr>
<td>Cascara Sagrada</td>
<td>Laxative</td>
<td>Hepatitis with cholestatic picture</td>
</tr>
<tr>
<td>Chaparral</td>
<td>Antioxidant and Snake bites</td>
<td>Cholestasis and chronic hepatitis</td>
</tr>
<tr>
<td>Dai Saiko-to (Chinese herb)</td>
<td>Immunostimulation</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Ephedra sinica (Ma Huang)</td>
<td>Weight loss</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Fleeceflower Root (Shou-Wu-Pian)</td>
<td>Various such as carbuncles, urticaria with itching and constipation</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Greater Celandine</td>
<td>Dyspepsia and Irritable Bowel Syndrome</td>
<td>Cholestatic hepatitis and fibrosis</td>
</tr>
<tr>
<td>Jin Bu Huan</td>
<td>Sedative and analgesic</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Margosa Oil</td>
<td>Arthritis and skin disorders</td>
<td>Reye’s syndrome</td>
</tr>
<tr>
<td>Mentha pulegium (pennyroyal)</td>
<td>Digestive disorders, liver and gallbladder disorders, gout</td>
<td>Fulminant hepatic failure</td>
</tr>
<tr>
<td>Pyrrolizinidine alkaloids (comfrey)</td>
<td>Herbal tea</td>
<td>Veno-occlusive disease of the liver</td>
</tr>
<tr>
<td>Psyllium seed husks (Isabgol)</td>
<td>Irritable bowel syndrome and constipation</td>
<td>Giant cell hepatitis</td>
</tr>
<tr>
<td>Piper methysticum (Kava roots)</td>
<td>Anxiolytic and sleeping aid</td>
<td>Acute hepatitis, cholestasis, fulminant hepatic failure</td>
</tr>
<tr>
<td>Scullcap</td>
<td>Wild mushroom, delicacy</td>
<td>Fulminant liver failure</td>
</tr>
<tr>
<td>Serenoa repens (Saw palmetto)</td>
<td>Benign Prostatic Hyperplasia</td>
<td>Mild hepatitis</td>
</tr>
<tr>
<td>Teucrium chamaedrys (Wall Germander)</td>
<td>Weight reduction</td>
<td>Hepatitis and fibrosis</td>
</tr>
<tr>
<td>Teucrium polium (Felty Germander)</td>
<td>Treatment of visceral pain, diabetes</td>
<td>Acute hepatic failure</td>
</tr>
<tr>
<td>Valerian root</td>
<td>Sleep aid</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Yohimbe</td>
<td>Sexual potency</td>
<td>Hepatitis??</td>
</tr>
</tbody>
</table>

* Other herbal products with possible hepatic toxicity are: Alpine Cranberry, Alkanna Borage, Cayenne, Colt’s Foot, Dong Quai, Dusty Miller, Forget-Me-Not, Groundsel, Hemp Agrimony, Hops, Life Root, Mercury Herb, Mistletoe, Monnon tea, Petasites, Pokerooot, Ragwort, Rue, Sassafrass, Schisandra, Sweet Clover, Tonka Beans, Trailing Arbutus, Uva Ursi, Witch Hazel, and Woodruff.

† List not meant to be all inclusive
Vaccination against hepatitis A and B has shown to be an effective means to prevent these cases in patients with CLD. All patients with CLD of any origin should be tested for antibodies for hepatitis A (total antibodies) and hepatitis B (only surface antibodies). If no sign of previous exposure is present, patients should be vaccinated (Figure 1). Hepatitis A vaccination consists of two intramuscular injections provided six months apart. The efficacy of this vaccination to produce antibodies is as high 100% of persons at 26 weeks and the second dose provides persistent immunity projected to last at least 20 years for normal and CLD subjects (43), with lower rates in patients with decompensated cirrhosis or immunocompromised state. The vaccine for hepatitis B should be provided in three doses (months 0, 1 and 6). Protective serum titers of more than 10 mIU per milliliter develop in 95% to 99% of healthy individuals; however, this response is

Figure 1. Algorithm of hepatitis vaccination for patients with chronic liver disease.

Vaccinate for Hep A.**

Vaccinate for Hep B.*

NO vaccine for Hep A.

NO vaccine for Hep B.

1. HAV Tot Ab (–)
2. HBs Ab (–)
3. HBc Ab (–)/(+)‡
4. Unknown†

1. HAV Tot Ab (+)
2. HBs Ab (+)
3. HBc Ab (–)/(+)

Hepatitis Serology needed for CLD:
1. HAV Tot Ab
2. HBs Ab
3. HBc Ab

1. HAV Tot Ab (–)
2. HBs Ab (+)
3. HBc Ab (–)/(+)

† For low risk patient population it is reasonable and cost effective to vaccinate without immune panel assessments
‡ If hepatitis B core antibody is positive but surface antibody is negative, attempt should be made to provide hepatitis B surface antibody with vaccination against hepatitis B.
* HBV vaccines consist of three injections scheduled at 0, 1 and 6 months.
** HAV vaccine consists of two injections six months apart.
reduced in persons that are over 40 years of age or are otherwise immunocompromised (44). These two vaccines can be administered in the same office visit at different sites or in a combined form. The safety of these vaccines in patients with CLD has been proven in multiple studies (45,46).

Hepatitis B carriers and their providers should be aware of the possibility of reactivation of HBV after immunosuppression as in chemotherapy, steroid use and transplantation. This issue is a major concern in recent years due to the usage of agents like infliximab for the treatment of autoimmune disorders like Crohn’s disease or Rheumatoid arthritis (47). Kohrt, et al, did a meta-analysis of 10 trials regarding usage of prophylaxis (with lamivudine) in these patients receiving chemotherapy. It was concluded from this study that patients with chronic HBV infection should be started on lamivudine prophylactically (if no contraindications) before chemotherapy administration and the duration of the therapy should not be less than 12 months (48).

LIVER DISEASE AND DIET/EXERCISE

In recent years, non-alcoholic fatty liver disease (NAFLD) has become the most common cause of CLD in the western world. The prevalence is estimated to be close to 34% of the adult population (49). The term fatty liver is defined as an accumulation of fat in the liver exceeding 5%–10% of its weight or as a percentage of fat-laden hepatocytes at light microscopy. NAFLD has been directly related to fat intake, diabetes mellitus, and obesity. Ueno, et al showed that a weight reduction program which includes diet and exercise could significantly improve liver function tests and liver histology in patients with fatty liver (50). Younossi, et al showed that obesity and subsequent presence of superimposed NASH were independently associated with a higher degree of liver fibrosis in patients with chronic hepatitis C (51). Bressler, et al also showed that obesity (defined as BMI higher than 30) is a negative predictor of response to hepatitis C treatment (52).

These studies suggest that a low fat diet and regular exercise could minimize hepatic steatosis and prevent further complication of CLD. A gradual weight reduction should be recommended to obese patients with CLD of any etiology.

Table 3
Summary of Evidence-based Recommendations for Patients with Chronic Liver Disease

- Alcohol abstinence
- Appropriate vaccination for hepatitis A and B (as per Figure 1)
- Avoidance of herbal products and other supplements with possible hepatotoxicity*
- Avoidance of over-the-counter products like NSAIDs*
- Avoidance of iron supplementation unless medically indicated*
- Avoidance of prescription drugs that are hepatotoxic
- Safety of acetaminophen in doses less than 2 grams daily
- Low fat, “heart smart” diet and exercise

*The thorough review of the usage of these products by the primary care physician is critical.

In summary, in CLD, secondary to long natural history, there is an opportunity to practice good preventive care. Table 3 provides a summary of the evidence-based preventive measures that are recommended to delay progression of CLD. Alcohol abstinence, immunization for hepatitis A and B, avoidance of toxins and weight control are the major strategies. Part II will address preventive approaches in those with compensated hepatic cirrhosis and part III will address preventive approaches of decompensated cirrhosis.

Reference

Preventive Approaches in Chronic Liver Diseases

A SPECIAL THREE-PART ARTICLE


