Natural Interventions for Treating Hepatitis C
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Chronic hepatitis C, caused by the hepatitis C virus (HCV), is occurring at epidemic proportions. It is estimated that 3.9 million individuals are infected in the United States. There are four times more people infected with HCV than with human immunodeficiency virus (HIV), with more than 170 million people infected with HCV worldwide. HCV is the most common cause of chronic liver disease, cirrhosis, and liver cancer in the Western hemisphere.

Current treatment prognosis with interferon (INF) results in a 15% to 30% response rate after one year. Studies have shown that of patients who exhibit viral clearance, 30% to 70% relapse in the first few months. A sustained response of at least six months occurs in only ten percent to 15% of patients.

The side effects of INF treatment include myalgia, fatigue, fever, headache, nausea, leukopenia, thrombocytopenia, alopecia, irritability, depression, thyroid abnormalities, pulmonary complications, and retinal damage. Many patients cannot function or work during treatment. This treatment decreases the risk of developing hepatocellular carcinoma only in sustained virologic responders.

While ribavirin significantly reduces the risk of not having a sustained virologic response by 26% to 66%, combination therapy with the antiviral and INF also increases the risk of treatment discontinuation. Side effects of combined treatment are "universal, significant, and possibly serious." Low tolerability and significant side effects of therapy frequently lead to dose reduction and treatment discontinuation, decreasing response rates further.

A newer form of INF - pegylated INF given with ribavirin - may produce responses in more than 50% of patients. INF is combined with polyethylene glycol (pegylated INF) to increase the level of the drug so it can be given just once per week, rather than the standard INF, which is administered three times per week. This may also cut down the days that patients experience the deleterious side effect of flu-like symptoms. However, INF is still administered with ribavirin, and the pegylated form has only recently been approved by the Food and Drug Administration (FDA). This treatment is extremely expensive and is not affordable for patients who do not have prescription drug coverage. For many patients, the available treatment options raise a question: Is the treatment worse than the disease?

Glycyrrhizin Compounds: Activities, Mechanisms, and Side Effects

Intravenous glycyrrhizin (GL) has been used for more than two decades in Japan as the approved drug Stronger Neo-Minophagen C (SNMC), produced by Minophagen Pharmaceuticals, Tokyo, Japan. The composition of each 2-mL ampule consists of 4 mg of monoammonium glycyrrhizinate (as glycyrrhizin), 40 mg of aminoacetic acid, 2 mg of L-cysteine HCl, and 1.6 mg of sodium sulfite. The 20-mL ampules, which are more commonly used, provide 40 mg of GL, 400 mg of glycine, and 20 mg of L-cysteine.

GL is a conjugate of glycyrrhetinic acid (GA) and glucuronic acid. Oral GL is metabolized in the intestines to GA. When intravenously administered, GL is metabolized as it is excreted through the bile into the intestines. GL and GA have similar properties.

Human studies have shown the safety and effectiveness of SNMC, oral GL, and GA for treating hepatitis A, B, and C; HIV (superior to zidovudine); Herpes (I, II, and H. zoster), Lichen planus, influenza, cytomegalovirus, and cancer. Personal clinical experience and letters to the editor appearing in various journals indicate applications for GL, GA, and SNMC for treating chronic fatigue and immune dysfunction, Epstein-Barr
Hepatitis C

> virus, condyloma, and other “viral” conditions. There are also reports that these substances may increase the effectiveness of INF therapy in patients for whom such treatment has failed.6-10

GL and GA have direct antiviral activity on some viruses such as HIV. However, with respect to orally, preventive treatment with potassium is prudent. While none of the studies reviewed used potassium with SNMC, it would be interesting to see if this would also help to prevent the side effects associated with pseudoaldosteronism.

Studies on SNMC and Sho-Saiko-To

A comparative study13 was conducted by dividing 100 cases at random (56.2%) from a total of 178 patients into two groups. Group A received 100 mL of SNMC per day, and Group B received 40 mL of SNMC per day for three weeks. The subjects had hepatitis C or hepatitis B, and many had cirrhosis. Forty-nine percent (47 of 93) of the patients had previously been treated with INF and had experienced no improvement of alanine aminotransferase (ALT). Patients were rated as “markedly improved” if their ALT levels dropped to <1.2 times the normal upper limit and as “improved” if their ALT levels dropped to <1.2-1.5 times the upper limit. Group A had a 52.3% improvement (23 of 44 cases), and Group B had a 26.1% improvement (12 of 26 cases). Group A had a significant improvement compared to Group B, confirming that higher therapeutic doses are needed for successful treatment.13

A correlation between improvement in ALT levels and histologic findings has been confirmed in many studies. Reduction in ALT level is the best prognostic factor, rather than viral load, with respect to subsequent development of liver cancer. For an earlier study,14 researchers retrospectively collected data on patients with HCV who were treated with SNMC for 15 years. Eighty-four patients received 100 mL/day of SNMC for eight weeks and were maintained on this dose two to seven times per week for two to 16 years. These patients were compared to a group of control subjects who only received various nutritional and botanical supplements. ALT levels fell to normal in 35.7% of the SNMC-treated group and in only 6.4% in the control group. At year 15, the rate of cirrhosis was only 21% in the SNMC-treated group, compared to 37% in the control group. Liver cancer rates were significantly lowered in the SNMC-treated group, with only a 12% occurrence compared to a 25% occurrence in the control group.14

While the exact botanical and nutritional supplements were not fully elucidated in this study, there are reports about established formulations, such as sho-saiko-to (a well-researched Kampo medicine). Sho-saiko-to has been used for treating various conditions, such as cancer. In a well-documented case report, a patient with chronic active HCV with elevated aspartate aminotransferase (AST) (63) and ALT (94) levels had a laparoscopy of the liver in 1986, revealing precirrhosis. By 1990, the patient’s liver enzyme levels rose to 323 (AST) and 349 (ALT), and the patient was given 5.4 g of sho-saiko-to orally per day. By 1992, this patient’s liver enzyme levels had dropped significantly to 57 (AST) and 61 (ALT), and he had 100 kcopies per mL of HC RNA. Progression to cirrhosis was confirmed via laparoscopy. The patient received INF for 24 weeks in 1992 and had no response. Liver-function tests showed elevated levels, and the HC RNA was still positive.

Beginning in 1997, 60 mL of SNMC, three times per day, was administered for two years. In 1999, the patient’s AST level dropped to 30, the ALT level dropped to 39, and the HC RNA was very low (3.2 kcopies/mL). INF was readministered, this time for 16 weeks, achieving a sustained response: all liver-function tests produced normal results, laparoscopic evaluation showed improvement, and the HC RNA remained negative.15 Patients with HCV genotype 1 are recognized as being nonresponders to

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HCV, these substances have indirect antiviral activity.10 They decrease cell-membrane permeability, thereby decreasing hepatocyte injury; inactivate the virus; and inhibit viral proliferation. These compounds also produce antioxidant activity. They also increase g-NF, T-cell, and natural-killer cell activity and numbers. What seems to make GA and GL exceptional is their ability to inhibit cytolytic reactivity of the complement system selectively. They inhibit cytolytic reactions selectively, leading to inflammatory host-cell injury (e.g., hepatocytes). They do not inhibit (but may rather enhance) the immune adherence responsible for immune phagocytosis and regulation of antibody production for creating protective immunity against invaders. These compounds also inhibit the arachidonic acid cascade (phospholipase A2).10

SNMC contains aminoacetic acid and L-cysteine for preventing pseudoaldosteronism. Aldosterone suppression may be caused by a rise in renal cortisol, resulting in sodium retention, potassium depletion, and hypertension.

Pseudoaldosteronism has rarely been reported at the therapeutic doses reviewed in this paper, but the disorder can be treated with spironolactone (a mineralocorticoid receptor antagonist).11,12 If it is used
INF therapy and as being difficult to treat.

Fifty-nine patients with this poor prognosis were included in an SNMC study that compared doses, administration periods, and active treatment vs. placebo. Administration of SNMC was compared three times per week to six times per week for a total of four weeks. Active treatment was also compared to a placebo. SNMC (with 80, 160, or 240 mg of GL) was administered either as an intravenous drip diluted with 100 mL of five-percent glucose for 15-20 minutes or undiluted and injected directly into a vein via a butterfly in three to five minutes (with 200 mg of GL). The dose of SNMC was tailored to the reduction in ALT in each subject.

The therapeutic schedule of SNMC was aimed at suppressing ALT levels lower than INF because they felt better during SNMC therapy. Persistently high ALT at >80 international units (IU)/L with HCV is associated with more rapid development of liver cancer than persistently low ALT levels of < 80 IU/L. The study researchers suggested that an oral GL or GA supplement should be investigated for maintenance therapy.16

A 15-year follow-up study was conducted to determine if SNMC could reduce the risk of liver cancer significantly in patients with HCV. The therapeutic schedule of SNMC was aimed at suppressing ALT levels below 75. Patients were given 40 mL of SNMC (with 80 mg of GL) five to six times per week. If ALT levels were lowered, then maintenance therapy was administered three times per week. If this dose failed, SNMC was increased to 100 mL (with 200 of mg GL) five to six times/week until the patients responded. The maintenance dose was tailored to keep ALT levels normal or close to normal. Liver cirrhosis occurred significantly less frequently in 178 patients on long-term SNMC than in 100 controls (28% v. 48%) at year 13. Liver cancer developed significantly less frequently in 84 patients on long-term SNMC than in 109 controls (13% vs. 25%) at year 15.

In this study, the researchers noted a linear relationship between the cumulative ALT score and the increase in the stage of fibrosis, irrespective of the stage of fibrosis found in the first biopsy. The higher the stage of fibrosis was in the first biopsy, the lower the cumulative ALT score required for progression to the next stage of fibrosis. To prevent progression, the cumulative ALT score needs to be kept increasingly lower as the stage of fibrosis increases. Incidence of liver cancer increases alongside of the mean ALT score.17

The effectiveness of 7.5 g of crude glycyrrhiza root concentrated to contain 750 mg of GL and given orally to 80 patients with chronic hepatitis B was the subject of another study. Acutely ill patients received the treatment for 30 days, and patients who were chronically ill received the treatment for 90 days. These two groups of patients were compared to identical groups of patients who received Poly I:C (thymosin, polyinosinic acid, and cytidylic acid). Each of the four groups was comprised of 20 patients.

More significantly, marked improvement in indices of liver function and negative conversion of hepatitis B surface antigen (HBsAg) and hepatitis B envelope antigen (HBeAg) were seen in the glycyrrhizin-treated group than in the control group. There was no seroconversion noted in the Poly I:C-treated groups. Among the patients who received the GL, the indices of liver function returned to normal in 85% of the subjects with acute hepatitis and 75% of those with chronic hepatitis. The subjects who received the Poly I:C had a reduction in 35% and ten percent, respectively, in control groups.18

The efficacy of sho-saiko-to was evaluated in 222 patients with chronic active hepatitis B in a double-blinded, multicenter clinical trial. One hundred and sixteen patients (116) received a daily oral dose of 5.4 g of the preparation for 12 weeks followed by the same dose for an additional 12 weeks. One hundred and six patients (106) received a placebo for 12 weeks, followed by a crossover to 0.5 g of sho-saiko-to for an additional 12 weeks. Serum AST and ALT levels decreased significantly with the administration of the preparation. The difference of the mean value between the treatment group and the placebo group was significant at 12 weeks. In patients with chronic active hepatitis B, a tendency toward a decrease of HBeAg and an increase of anti-HBe-antibodies was also observed. No remarkable side effects were noticed.19

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Antioxidant Treatment for Hepatitis C

For a case study, three patients were selected randomly from a pool of 50 patients with cirrhosis, portal hypertension, and esophageal varices secondary to chronic HCV infection. The patients received daily divided doses of 600 mg of alpha-lipoic acid, 900 mg of silymarin (milk thistle [Silybum marianum] seed), 400 mcg of selenium, 200 mg of a vitamin B complex formula, 1-6 g of vitamin C, 400 IU of vitamin E, and a multimineral preparation. This protocol was chosen to protect the liver from oxidative damage, increase levels of fundamental antioxidants, and interfere with viral replication. The subjects were instructed to eat six servings of fruit and vegetables per day, to restrict their meat intake to four ounces or less per meal, and to drink eight glasses of purified water per day. Stress reduction and exercise were also encouraged.

Phyllanthus Treatment of Hepatitis

The Phyllanthus species includes P. niruri, P. amarus, and P. urinaria. P. amarus is the most common form found as a dietary supplement. In a study on Phyllanthus, 123 patients with chronic hepatitis B were divided into groups who received different species. Eleven subjects received P. amarus, 42 received P. niruri, 35 received P. urinaria, and 35 received no therapy. This study was conducted to ascertain if different Phyllanthus species have different therapeutic effects in patients with hepatitis B. Each group was randomly assigned to receive an herb for three months. Treatment regimens were as follows: P. amarus, 500 mg, three times per day; P. niruri and P. urinaria, 300 mg, three times per day (month 1), 600 mg, three times per day (month 2), and 900 mg, three times per day (month 3). Patients who received P. urinaria were more likely to lose detectable HB e-antigen from their sera and more likely to have their HB e-antibody status seroconvert from negative to positive compared to the patients who received the other preparations. There was a statistically significant decrease in GGT levels in the group treated with P. amarus. A systematic review of 22 randomized clinical trials for Phyllanthus treatment of hepatitis B was conducted. The combined results showed that Phyllanthus had a positive effect on clearance of HBsAg. No significant differences in clearing of HBsAg, HBeAg, and HBV DNA were demonstrated compared to the results of treating patients with INF alone. However, Phyllanthus has significant antiviral activity and was superior to INF for achieving ALT level normalization. P. amarus and P. urinaria had positive effects on HBsAg/HBeAg clearance, and only P. urinaria had positive effects on HBV DNA clearance.

Discussion

Given the prior history of use of SNMC and the wealth of scientific data, there is no rational reason for this not being an approved treatment in the United States for hepatitis. Numerous studies have confirmed the failure and dropout rates that result from available treatment with INF, with or without ribavirin, as well as poor-to-moderate response rates, although it has been suggested among researchers that using pegylated INF may raise response rates. However, no long-term studies exist on any of the available conventional therapies. Most studies are, at best, 48 months in duration with follow-ups that occur one year after treatment cessation. Interestingly, some studies on conventional treatment suggest that, in responders, liver cancer may be prevented, but there are no studies on conventional treatment that even approach the 15-year study on SNMC. Many patients refuse treatment when potential side effects of conventional treatment are disclosed, and many patients drop out of treatment as a result of serious and incapacitating side effects.

The data suggest that pretreatment with SNMC may even enhance INF treatment. GL appears to work orally as well, and further studies are needed to ascertain if long-term treatment would be maintained better with initial intravenous administration of SNMC with long-term oral supplementation with GL and/or GA. Yet, with excellent results reported for patients with hepatitis B who were given GL, the question remains as to why those studies were not repeated for patients with HCV. And why was this not done for sho-saiko-to?

Could patients who cannot respond to intravenous infusions be treated as effectively with oral preparations of...
The most compelling data presented is the fact that significant numbers nonresponders with genotype 1 (nonresponders to INF) responded to SNMC. To date, there is no pharmaceutical available that has been shown to reduce the occurrence rate of liver cancer as significantly as SNMC. In addition, there are no pharmaceuticals with a 13-15-year follow-up study on patients with HCV or any other type of hepatitis, nor are there any pharmaceuticals that are as inexpensive as all the herbal and antioxidant treatments combined.

The antioxidant treatment of HCV20 yielded excellent results in a small but well-designed pilot study. The data on silymarin was compelling enough to grant an investigational new drug status to study the herb's use for treating HCV. It is clear from the available data that ALT, rather than viral load, is the determining factor for fibrosis, cirrhosis, and liver cancer. It appears that SNMC, GA/GL, the dietary supplements used as the protocol in the antioxidant treatment of HCV and silymarin, are all able to lower ALT levels significantly. The study that used multiple antioxidants also incorporated diet therapy, stress reduction, and exercise. These are key lifestyle components that also may have enhanced the effectiveness of the treatment.

The most important questions arise regarding the Phyllanthus species: which one? and what dosage is effective? The results reported with hepatitis B appeared to be, for the most part, outstanding; yet, there were no follow-up studies for HCV. In the study that used therapeutic regimens of different types of Phyllanthus species (P. amarus, P. niruri, and P. urinaria), it appears that P. amarus and P. urinaria were the most effective. However, why was a lower dose of P. amarus used compared to the other Phyllanthus species used in this study? The study authors explained that they chose the doses based on historical data. However, it would be interesting to see this type of study repeated for patients with HCV who would be given 900 mg, three times per day, of both P. amarus and P. urinaria. The systematic review also confirmed that P. urinaria and P. amarus were the most effective for treating hepatitis B. Overall, it appears that herbs that were effective for treating hepatitis B are also effective for treating HCV.

Conclusions
For patients for whom INF therapy has failed, it appears prudent to use a protocol with absolutely no downside. There are no serious side effects reported for any of the botanicals or antioxidants reviewed in this paper. While oral GA/GL supplements can be found, SNMC is not approved for use in the United States. For patients who refuse INF therapy, there appears to be other substances that may yield equal, if not better, results for long-term treatment. If the goal of treatment is to prevent progressive liver disease and liver cancer and to have patients feel well and be productive, it appears that many of the substances reviewed offer a rational approach for treatment. More research is sorely needed to see what combination of substances will yield the best results in the long term. We are able to determine this through liver-function tests, liver biopsies, viral load tests, and quality of life as reported by patients.

New York University Medical Center's Infectious Disease Research Group, New York City, recently confirmed in a personal communication that a study of this type should be underway in the near future.


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Notes

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Hepatitis C
