

Hepatitis C

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ABSTRACTS

[Stimulation of regenerative processes and correction of the functional activity of the liver in its partial resection and toxic lesions].

Abakumova OI, Kutsenko NG, Fedorova LM, et al.

Vestn Ross Akad Med Nauk. 1996;(5):36-41.

The effects of hepatotropic growth factors (HGFs) and phospholipid drugs on the recovery of functions and the regeneration of the rat liver were studied in CC14-induced toxic damage and after partial hepatectomy (PHE). HGFs isolated from the cytoplasmic cells of the regenerating liver, as well as from the liver of the animals given prodigiozan and from the media taken after culturing the explants of the regenerating liver were found to stimulate DNA synthesis and hepatocytic proliferation following PHE and in the cirrhotic liver. Prodigiozan was shown to induce the formation of HGFs not only in the rat liver following PHE, but in the liver of intact animals. It was established that the covalently binding complex of albumin and bilirubin stimulated the synthesis of proteins and DNA in the regenerating liver, but non-covalently binding complex inhibited these processes. When CC14 was administered to the animals, the two complexes enhanced the reparative synthesis of DNA, without changing the level of replicating synthesis, the non-covalently binding complex completely eliminating the single-strand breaks in DNA. Phospholipid agents containing soybean and sunflower phosphatidylcholines increased the synthesis of RNA and albumin, which were decreased due to exposure to CC14 and had the property of stimulating the synthesis of total DNA and considerably enhancing that of mitochondrial DNA

Profile of hepatitis C virus and the possible modes of transmission of the virus in the Gizan area of Saudi Arabia: a community-based study.

al Faleh FZ, Ramia S, Arif M, et al.

Ann Trop Med Parasitol. 1995 Aug; 89(4):431-7.

The seroprevalence of antibody to hepatitis C virus (anti-HCV) and the possible modes of transmission of HCV were investigated in Gizan, southern Saudi Arabia. The sample size chosen to give an adequate estimate of the seroprevalence, about 1500, was based on the assumption that 5% of the population in Gizan were anti-HCV-positive. Sera from 1482 subjects (705 males, 777 females; aged > or = 10 years) were initially screened for anti-HCV using a commercial, ubiquitin-based enzyme immunoassay. Repeatedly reactive sera were confirmed positive using second-generation immunoassays. Serum samples were also tested by ELISA for hepatitis B surface antigen (HbsAg) and antibodies to this antigen and to the hepatitis B core antigen. Of the subjects tested, 27 (1.8%) were anti-HCV-positive. Exposure to HCV was generally similar in both sexes, age-prevalence curves for anti-HCV peaking in males aged > 49 years (6.2%) and in females aged 40-49 years (5.0%). In the youngest subjects, those aged 10-19 years, the HbsAg carrier rate was significantly higher in males (10.4%) than in females (3.6%). Exposure to the hepatitis B virus was similar in both sexes (31.0% in males v. 28.6% in females). Some 7.4% and 14.8% of the 27 anti-HCV-positive cases had histories of schistosomiasis and blood transfusion, respectively. The corresponding values for the 1455 anti-HCV-negative cases investigated, 1.1% for schistosomiasis and 3.5% for blood transfusion, were much lower. The spouses and other family members of eight anti-HCV-positive index cases were investigated but none was anti-HCV-positive.(ABSTRACT TRUNCATED AT 250 WORDS)

Natural history of hepatitis C virus infection.

Amarapurkar D.

J Gastroenterol Hepatol. 2000 May; 15 Suppl:E105-E110.

Hepatitis C is a heterogeneous disease whose natural history is controversial and perplexing. However, it can be a pernicious disease and is responsible for considerable mortality and morbidity. More than 80% individuals infected with the hepatitis C virus (HCV) develop chronic infection; the remaining 10-20% develop spontaneous clearance with natural immunity. The majority of

patients who develop chronic HCV infection are asymptomatic; but 60-80% develop chronic hepatitis as indicated by elevated ALT; around 30% maintain normal ALT. One-third of chronically infected patients develop progressive liver injury, fibrosis and cirrhosis over a period of 20-30 years, and 15% develop hepatocellular carcinoma. Acquiring infection after the age of 40 years, male sex, excessive alcohol-consumption, HBV or HIV co-infection and the immunosuppressive state have been identified as factors associated with progression of fibrosis and development of cirrhosis. The relationship between virus load, HCV genotype I and quasispecies variability and progression of liver disease is controversial. In the present study on 141 patients with chronic HCV infection and established chronic liver disease, the median time to develop cirrhosis was 20 years. Progression to cirrhosis was faster (16 vs 20 years) in those who acquired infection after the age of 35 years, and in immunosuppressed patients (8 vs 21 years), whereas diabetes, sex and HBV co-infection were not associated with faster progression

Watch.

Anon.

Anon J. 2001 21

Rational design of a potent, long-lasting form of interferon: a 40 kDa branched polyethylene glycol-conjugated interferon alpha-2a for the treatment of hepatitis C.

Bailon P, Palleroni A, Schaffer CA, et al.

Bioconjug Chem. 2001 Mar; 12(2):195-202.

A potent, long-lasting form of interferon alpha-2a mono-pegylated with a 40 kilodalton branched poly(ethylene glycol) was designed, synthesized, and characterized. Mono-pegylated interferon alpha-2a was comprised of four major positional isomers involving Lys31, Lys121, Lys131, and Lys134 of interferon. The in vitro anti-viral activity of pegylated interferon alpha-2a was found to be only 7% of the original activity. In contrast, the in vivo antitumor activity was severalfold enhanced compared to interferon alpha-2a. Pegylated interferon alpha-2a showed no immunogenicity in mice. After subcutaneous injection of pegylated interferon alpha-2a, a 70-fold increase in serum half-life and a 50-fold increase in mean plasma residence time concomitant with sustained serum concentrations were observed relative to interferon alpha-2a. These preclinical results suggest a significantly enhanced human pharmacological profile for pegylated interferon alpha-2a. Results of Phase II/III hepatitis C clinical trials in humans confirmed the superior efficacy of pegylated interferon alpha-2a compared to unmodified interferon alpha-2a

Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial.

Bodenheimer HC, Jr., Lindsay KL, Davis GL, et al.

Hepatology. 1997 Aug; 26(2):473-7.

Hepatitis C is a common cause of chronic liver disease that may progress to cirrhosis. We conducted a multicenter double-blind placebo-controlled trial of ribavirin 600 mg given orally twice daily for 36 weeks with follow-up off therapy for an additional 16 weeks. Fifty-nine patients with compensated chronic hepatitis C were entered. Efficacy was measured at the end of therapy and after follow-up by normalization of alanine aminotransferase (ALT), improvement in liver histology, reduction in hepatitis C virus (HCV) RNA level and improvement of symptoms. Among the ribavirin recipients, 12 of 29 (41.4%) had normal ALT values at 36 weeks compared with only 1 of 30 (3.3%) placebo recipients ($P < .001$). No patient maintained a normal ALT when therapy was stopped. No significant decrease in level of HCV RNA was observed during the study. Histological improvement among subjects who normalized ALT (-1.67 Knodell index) was significantly greater than that in other treated patients (+0.33 Knodell index; $P < .05$). Fatigue improved in 19.2% of ribavirin-treated subjects and in 8.3% of placebo recipients whereas no worsening of fatigue was reported by ribavirin recipients compared with 16.7% of controls. This difference in fatigue was significant at weeks 36 and 52 ($P < .05$; $.02$, respectively). Adverse events were generally comparable between treatment groups except for a reversible hemolytic anemia experienced by ribavirin recipients. Chest pain was noted in four patients on ribavirin. Ribavirin was well tolerated and improved aminotransferase values and reduced fatigue in patients with hepatitis C viral infection while treatment was being administered. Because this action was produced without change in viral level, the mechanism of action of this agent requires further investigation

The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders.

Bottiglieri T, Hyland K, Reynolds EH.

Drugs. 1994 Aug; 48(2):137-52.

This review focuses on the biochemical and clinical aspects of methylation in neuropsychiatric disorders and the clinical potential of their treatment with ademetionine (S-adenosylmethionine; SAMe). SAMe is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters. The synthesis of SAMe is intimately linked with folate and vitamin B12 (cyanocobalamin) metabolism, and deficiencies of both these vitamins have been found to reduce CNS SAMe concentrations. Both folate and vitamin B12 deficiency may cause similar neurological and psychiatric disturbances including depression, dementia, myelopathy and peripheral neuropathy. SAMe has a variety of pharmacological effects in the CNS, especially on monoamine neurotransmitter metabolism and receptor systems. SAMe has antidepressant properties, and preliminary studies indicate that it may improve cognitive function in patients with dementia. Treatment with methyl donors (betaine, methionine and SAMe) is associated with remyelination in patients with inborn errors of folate and C-1 (one-carbon) metabolism. These studies support a current theory that impaired methylation may occur by different mechanisms in several neurological and psychiatric disorders

Liver iron concentration and distribution in chronic hepatitis C before and after interferon treatment.

Boucher E, Bourienne A, Adams P, et al.

Gut. 1997 Jul; 41(1):115-20.

BACKGROUND: Recent studies have suggested that, in patients with chronic hepatitis C, elevated iron stores are predictive of a poor response to interferon. **AIMS:** To assess liver iron concentration and distribution before and after interferon treatment in patients with hepatitis C in order to evaluate further the role of iron in the pathogenesis of hepatitis C. **PATIENTS:** Fifty-five patients with hepatitis C treated with alpha interferon for six months. **METHODS:** Patients were evaluated for liver iron concentration (normal value < 36 $\mu\text{mol/g}$), and liver iron distribution before and six months after therapy. **RESULTS:** At entry: liver iron concentration was elevated in 16/55 patients (29%); iron staining (Perls' staining) was found in 31/55 patients (56%) mainly within Kupffer and endothelial cells. Iron load was significantly higher in patients with the most histological inflammatory activity. Following treatment: liver iron concentration decreased significantly (40 (24) to 30 (17) $\mu\text{mol/g}$, $p = 0.001$); this was related to iron depletion in mesenchymal cells. Iron depletion occurred regardless of the response to therapy. Elevated liver iron concentration was not found to be a predictive factor of failure of interferon. **CONCLUSION:** Although liver iron stores were usually normal or only slightly elevated in patients with chronic hepatitis C, biochemical and histological liver iron content decreased following treatment due to the diminution in mesenchymal iron deposits. Iron depletion was interpreted as both a consequence of the anti-inflammatory effect of treatment and a factor of improvement in liver histology

Hepatitis C infection in liver transplantation.

Charlton M.

Am J Transplant. 2001 Sep; 1(3):197-203.

Hepatitis C-associated liver failure is the most common indication for liver transplantation and recurs nearly universally following transplantation. Histological evidence of recurrence is apparent in approximately 50% of HCV-infected recipients in the first postoperative year. Approximately 10% of HCV-infected recipients will die or lose their allograft secondary to hepatitis C-associated allograft failure in the medium term. While the choice of calcineurin inhibitor and/or the use of azathioprine have not been clearly shown to affect histological recurrence of hepatitis C or the frequency of rejection in hepatitis C-infected recipients, cumulative exposure to corticosteroids is associated with increased mortality, higher levels of HCV viremia and more severe histological recurrence. In contrast to nonhepatitis C-infected recipients, treatment for acute cellular rejection is associated with attenuated patient survival among recipients with hepatitis C. The development of steroid-resistant rejection is associated with a greater than five-fold increased risk of mortality in HCV-infected liver transplant recipients. In lieu of large studies in a post-transplant population therapy with pegylated interferon (+/- ribavirin) should be considered in recipients with histologically apparent recurrence of hepatitis C before total bilirubin exceeds 3 mg/dL. The role of hepatitis C immunoglobulin and new immunosuppression agents in the management of post-transplant hepatitis C infection is still evolving. Overall, HCV-infected recipients who undergo retransplantation experience 5-year patient and graft survival rates that are similar to recipients undergoing retransplantation who are not HCV-infected

Combination therapy for chronic hepatitis C: interferon and ribavirin.

Christie JM, Chapman RW.

Hosp Med. 1999 May; 60(5):357-61.

Hepatitis C virus (HCV) infection is one of the commonest causes of liver cirrhosis and hepatocellular carcinoma. This review deals with treatment of chronic HCV infection with a combination of interferon and ribavirin. Recent trials have shown that approximately 40% of patients will clear HCV with combination treatment. This is an important advance in the treatment of this

serious viral infection

Hepatitis C.

Costa MA, Schiff ER.

Curr Treat Options Gastroenterol. 1999 Dec; 2(6):481-90.

End-stage liver disease due to chronic hepatitis C is the leading indication for orthotopic liver transplantation in the United States. Twenty percent to 30% of hepatitis C patients are at increased risk of developing cirrhosis, and 1% to 4% of cirrhotic patients will develop hepatocellular carcinoma. These findings warrant treatment for hepatitis C virus (HCV)-infected patients. Currently, the mainstay in treatment of HCV is the use of recombinant alpha interferon, or its equivalent, in combination with the oral antiviral agent ribavirin. The major goals of therapy are clearance of the virus, achieving a noninfectious state, and halting the necro-inflammatory process that leads to fibrosis and progression to cirrhosis. End of treatment response (ETR) is biochemical and virological remission-- normalization of serum aminotransferase (ALT) and undetectable levels of HCV RNA, at the end of therapy. Sustained virological response (SVR) is defined as the absence of viremia and persistently normal aminotransferase 6 months off treatment, and is the ultimate goal of therapy. Patients who achieve SVR will have significant and persistent histologic improvement. HCV genotype, pretreatment levels of HCV-RNA (viral load), the presence of advanced fibrosis or cirrhosis, gender, and age are independent predictors of response. Ribavirin is teratogenic, therefore, contraception is mandatory for both males and females during and up to 6 months after therapy. Side effects of combination therapy are dose-dependent and most commonly include symptoms of irritability, depression and fatigue, and laboratory evidences of leukopenia, thrombocytopenia, and hemolytic anemia

High rate of sustained response to consensus interferon plus ribavirin in chronic hepatitis C patients resistant to alpha-interferon and ribavirin: a pilot study.

da Silva LC, Bassit L, Ono-Nita SK, et al.

J Gastroenterol. 2002; 37(9):732-6.

BACKGROUND: The aim of this study was to evaluate an alternative treatment (consensus interferon plus ribavirin) for chronic hepatitis C patients resistant to combined therapy. **METHODS:** Fourteen patients previously resistant to interferon alpha plus ribavirin were consecutively assigned to receive 15 microg of consensus interferon plus ribavirin (1000 mg) daily for 4 weeks, and 9-15 microg every other day plus daily ribavirin for the following 44 weeks. Alanine aminotransferase and hepatitis C virus (HCV) RNA (Amplicor Monitor; Roche) levels were monitored during therapy and for 24 weeks after its completion. **RESULTS:** A rapid and marked decrease of HCV RNA viremia of more than 2 logs was observed in 10 (71%) of 14 patients at week 2 of treatment. At the end of therapy, 10 (71%) of 14 patients had undetectable HCV RNA. The end-of-treatment response rates were 6 of 9 (67%) patients for genotype 1 and 4 of 5 (80%) for other genotypes. Sustained response was observed in 4 (36%) of 11 patients who completed 24 weeks of follow-up. **CONCLUSIONS:** A marked and rapid decrease of viral load was observed during therapy with high doses of consensus interferon plus ribavirin in patients previously resistant to combined therapy, even in those infected with genotype 1. Of 11 patients who completed the post-treatment follow-up, 36% presented a sustained response

Daily or three times per week interferon alpha-2b in combination with ribavirin or interferon alone for the treatment of patients with chronic hepatitis C not responding to previous interferon alone.

De L, V, Trimoulet P, Winnock M, et al.

J Hepatol. 2002 Jun; 36(6):819-26.

BACKGROUND/AIMS: We compared the efficacy and safety of the combined therapy of daily interferon alpha-2b and ribavirin with those of interferon alpha-2b three times per week alone or in combination with ribavirin in non-responder patients with hepatitis C virus (HCV) infection. **METHODS:** A total of 376 patients were randomly assigned to receive interferon alpha-2b (6 MU three times per week for 24 weeks followed by 3 MU three times per week for 24 weeks) alone (group A) or in combination with ribavirin for 48 weeks (group B), or daily interferon alpha-2b (3 MU per day for 24 weeks followed by 3 MU three times per week for 24 weeks) and ribavirin (group C). **RESULTS:** After 24 weeks of therapy, HCV RNA was undetectable in 11.7, 24.0, and 37.8% for groups A, B, and C, respectively. Sustained virological response was more frequent in patients who received combination therapy with three times weekly interferon (20.9%) or daily interferon (26.0%) than in patients who received interferon alone (5.8%) ($P < 0.001$). The predictive HCV parameters for sustained response were a low viral load on day 7 and a negative HCV RNA on week 12. **CONCLUSIONS:** In conclusion, in non-responder patients with chronic hepatitis C, virological response with daily interferon and ribavirin, compared to interferon monotherapy, was significantly improved during treatment, although sustained virological response was similar for both combination therapies with ribavirin and three times a week or daily interferon

Hepatitis C and hepatocellular carcinoma.

Di Bisceglie AM.

Hepatology. 1997 Sep; 26(3 Suppl 1):34S-8S.

Hepatitis C virus (HCV) infection is now recognized to be a major risk factor for hepatocellular carcinoma (HCC), evidenced by finding both antibody to HCV (anti-HCV) and HCV RNA in serum of a substantial proportion of patients with HCC around the world and by the progression of liver disease to cirrhosis and HCC in individual patients infected with HCV. There seems to be an incubation period of two to three decades on average in most cases of HCV-related HCC. HCV infection usually results in development of HCC via cirrhosis, although the possibility of direct carcinogenic effects of HCV is still under study. Possible additional risk factors include infection with HCV genotype 1b, alcohol consumption, and co-infection with the hepatitis B virus. Estimates of the development of HCC among patients with cirrhosis of all types range between 1% and 4% per year. Assuming that 20% of patients with chronic hepatitis C go on to develop cirrhosis over a 10-year period, between 1.9% and 6.7% of all patients with chronic hepatitis C can be expected to develop HCC over the first two decades of infection. Although tests are available to screen for early HCC, the results of treating these small tumors have been disappointing. Thus, it is imperative that cost-effective means be developed for screening and prevention of HCV-related HCC

Sexual and perinatal transmission of hepatitis C.

Dienstag JL.

Hepatology. 1997 Sep; 26(3 Suppl 1):66S-70S.

Such nonpercutaneous routes of hepatitis C virus (HCV) transmission as sexual and perinatal spread are relatively inefficient. Several observations have been cited to support a role for sexual transmission of hepatitis C. Approximately 10% of persons with reported cases of acute hepatitis C in the United States report a history of potential sexual exposure. Anecdotal cases of sexual transmission have been reported, and HCV nucleotide sequence homology has been observed in viral isolates from sexual partners. Similarly, the prevalence of HCV infection is increased in groups with a high risk of exposure to sexually transmitted viral infections. Other observations, however, weigh against sexual transmission of HCV infection. Sexual transmission is negligible in sex-partner studies; alternative risk factors account for many cases of apparent sexual transmission between sexual partners; the prevalence of HCV infection in high-risk groups is much lower than that of other sexually transmitted infections; and the risk of apparently sexually transmitted HCV infection does not always correlate with intensity and duration of sexual exposure. The United States Public Health Service has estimated that the risk of sexual transmission is approximately 5%, well below the risk of sexual transmission of hepatitis B or human immunodeficiency virus (HIV). Similarly, perinatal HCV infection, though documented to occur, is unusual, except in babies born to mothers with very high levels of HCV RNA, including mothers with concomitant HIV infection. Weighing many, often conflicting reports, the United States Public Health Service has estimated that the likelihood of perinatal infection is low, on the order of 5% to 6%, and that breast feeding does not increase the risk of HCV infection in infants of mothers with hepatitis C. Current data do not support household exposure as a risk for HCV infection

Evaluation of antibodies to hepatitis C virus in a study of transfusion-associated hepatitis.

Esteban JI, Gonzalez A, Hernandez JM, et al.

N Engl J Med. 1990 Oct 18; 323(16):1107-12.

BACKGROUND. The hepatitis C virus (HCV) is now known to be the chief cause of transfusion-associated non-A, non-B hepatitis, but the prevalence of HCV among blood donors and the frequency of transmission by blood transfusion are unknown. **METHODS.** To assess the sensitivity and specificity of a test for antibody to HCV, we tested serum samples from participants in a large study of transfusion-associated hepatitis. Samples were obtained prospectively from consecutive adults undergoing open-heart surgery in Spain, but were tested retrospectively, after the antibody enzyme immunoassay for anti-HCV became available. **RESULTS.** Of 280 transfusion recipients given a total of 1109 units of blood, 27 (9.6 percent) had transfusion-associated non-A, non-B hepatitis (mean follow-up, 52 weeks) and 24 of the 27 seroconverted to anti-HCV-positive, whereas only 2 (0.8 percent) of the remaining transfusion recipients seroconverted. Among the 1044 donor specimens available for testing, 16 (1.5 percent) had anti-HCV antibody. Only 1 additional seropositive donor was found when 44 implicated donors who had been seronegative were retested 9 to 12 months later. Of the 16 recipients of anti-HCV-positive blood, 14 (88 percent) had transfusion-associated hepatitis and seroconverted to anti-HCV-positive. The remaining two recipients had neither hepatitis nor anti-HCV antibody. Among 25 patients with non-A, non-B hepatitis for whom all transfused blood was tested, 14 had received blood positive for anti-HCV. **CONCLUSIONS.** About 90 percent of blood donors with antibody to HCV have infectious virus in their blood. The screening of blood donors for anti-HCV antibody should prevent about half the cases of transfusion-associated

hepatitis, but the donors with infectious virus who are anti-HCV-negative may remain seronegative for prolonged periods

Liver iron influences the response to interferon alpha therapy in chronic hepatitis C.

Fargion S, Fracanzani AL, Sampietro M, et al.

Eur J Gastroenterol Hepatol. 1997 May; 9(5):497-503.

OBJECTIVE: To define whether there is any relation between the iron status of patients with hepatitis C virus (HCV) chronic liver disease and their response to interferon therapy. **DESIGN:** To evaluate the long-term response to 1 year of interferon therapy with addition of phlebotomies after 3 months of treatment if at that time alanine aminotransferase (ALT) had not normalized in a group of patients with HCV-positive chronic liver disease whose iron status had been characterized. **SETTING:** A northern Italian hospital. **PARTICIPANTS:** Fifty-eight anti-HCV-positive patients (four HCV-RNA negative) with biopsy proven chronic hepatitis and no evidence of iron overload as indicated by normal transferrin saturation at the time of enrollment in the study. **INTERVENTION:** Three times a week intramuscular injection of alpha interferon 3 MU for 1 year with addition of phlebotomies (350 ml/week) till iron depletion if after 3 months of interferon therapy ALT had not normalized. **RESULTS:** A long-term response was observed in 19 of the 52 patients who completed the treatment, four HCV-RNA negative and 15 positive. The four RNA-negative and seven of the 15 RNA-positive long-term responders had been treated with interferon alone, and the other eight also with phlebotomies. At univariate analysis only HCV genotype, gamma-glutamyltranspeptidase and liver iron concentration were significantly associated with response whereas sinusoidal iron deposition was of borderline significance. No association was found with sex, age, duration of disease, histology, Knodell score, transferrin saturation %, serum ferritin, hepatocytic iron score, and portal iron score. HCV-RNA serum levels, measured in 29 patients, did not correlate with response. At multivariate analysis liver iron concentration was still significant and one unit reduction of liver iron concentration (natural logarithm transformed) was associated with 2.95 odds ratio of response. **CONCLUSION:** These results indicate that iron in the liver is more closely related to response to interferon than the other variables considered, including HCV characteristics

A pilot randomized, controlled trial of the effect of iron depletion on long-term response to alpha-interferon in patients with chronic hepatitis C.

Fong TL, Han SH, Tsai NC, et al.

J Hepatol. 1998 Mar; 28(3):369-74.

BACKGROUND/AIMS: Some studies have suggested that hepatic iron may influence the response to interferon therapy in chronic hepatitis C patients. We conducted this randomized, controlled trial to evaluate the effect of iron depletion on: (1) aminotransferase activity and hepatitis C RNA levels; and (2) response to interferon therapy in 38 patients with elevated alanine aminotransferase levels and who were HCV RNA positive. **METHODS:** Seventeen patients underwent a 500-ml phlebotomy every 2 weeks until iron deficiency was achieved. Patients were then started on a 6-month course of alpha-interferon 2b (3 mu tiw). Controls were 21 patients who were monitored for a 6- to 8-week period without phlebotomy prior to interferon therapy. Response to interferon was defined as loss of serum HCV RNA by reverse transcriptase-polymerase chain reaction. Serum HCV RNA was quantitated by bDNA technique. **RESULTS:** Alanine aminotransferase levels decreased in 15/17 patients after phlebotomy. Mean alanine aminotransferase fell from 156.8 to 89.7 U/l ($p=0.008$). Changes in iron indices and alanine aminotransferase after phlebotomy were not accompanied by changes in HCV RNA levels. In control patients, neither alanine aminotransferase nor HCV RNA levels changed during the observation period. At the end of 24 weeks of interferon therapy, 7/17 phlebotomized patients had a response, compared to 6/21 control patients ($p=ns$). After 6 months of follow-up, 5/17 phlebotomized patients remained HCV RNA negative, in contrast to only 1/21 controls ($p=0.07$). **CONCLUSIONS:** Iron depletion led to a reduction in aminotransferase levels; this was not accompanied by changes in levels of hepatitis C RNA. There may be an improvement in the sustained response to interferon therapy, but this requires confirmation

Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection.

Fried MW, Shiffman ML, Reddy KR, et al.

N Engl J Med. 2002 Sep 26; 347(13):975-82.

BACKGROUND: Treatment with peginterferon alfa-2a alone produces significantly higher sustained virologic responses than treatment with interferon alfa-2a alone in patients with chronic hepatitis C virus (HCV) infection. We compared the efficacy and safety of peginterferon alfa-2a plus ribavirin, interferon alfa-2b plus ribavirin, and peginterferon alfa-2a alone in the initial treatment of chronic hepatitis C. **METHODS:** A total of 1121 patients were randomly assigned to treatment and received at least one dose of study medication, consisting of 180 microg of peginterferon alfa-2a once weekly plus daily ribavirin (1000 or 1200 mg, depending on body weight), weekly peginterferon alfa-2a plus daily placebo, or 3 million units of interferon alfa-2b thrice weekly

plus daily ribavirin for 48 weeks. RESULTS: A significantly higher proportion of patients who received peginterferon alfa-2a plus ribavirin had a sustained virologic response (defined as the absence of detectable HCV RNA 24 weeks after cessation of therapy) than of patients who received interferon alfa-2b plus ribavirin (56 percent vs. 44 percent, $P < 0.001$) or peginterferon alfa-2a alone (56 percent vs. 29 percent, $P < 0.001$). The proportions of patients with HCV genotype 1 who had sustained virologic responses were 46 percent, 36 percent, and 21 percent, respectively, for the three regimens. Among patients with HCV genotype 1 and high base-line levels of HCV RNA, the proportions of those with sustained virologic responses were 41 percent, 33 percent, and 13 percent, respectively. The overall safety profiles of the three treatment regimens were similar; the incidence of influenza-like symptoms and depression was lower in the groups receiving peginterferon alfa-2a than in the group receiving interferon alfa-2b plus ribavirin. CONCLUSIONS: In patients with chronic hepatitis C, once-weekly peginterferon alfa-2a plus ribavirin was tolerated as well as interferon alfa-2b plus ribavirin and produced significant improvements in the rate of sustained virologic response, as compared with interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone

[Role of ribavirin in the treatment of chronic hepatitis B].

Galban GE, Vega SH, Gra OB, et al.

Gastroenterol Hepatol. 2000 Apr; 23(4):165-9.

AIM: To evaluate the safety and efficacy of 1,200 mg/day of ribavirin for 6 months in the treatment of chronic hepatitis B. MATERIALS AND METHODS: An open study was carried out with 25 patients with chronic hepatitis B who had previously received placebo (first phase) as part of a randomized, double blind study and who remained HBeAg and HBV DNA positive. In the second phase they received oral ribavirin (1,200 mg/day) for 24 weeks and the results of the first phase were compared with those of the second. All the patients had a recent histological diagnosis and were anti-HCV and anti-HIV negative. In both phases clinical and laboratory evaluations were carried out at weeks, 0, 4, 8, 12, 16, 24, 32, 40 and 48 which included blood tests, liver function tests and serological markers of HBV, and HBV DNA when HBeAg became negative. Liver biopsy was performed at the beginning of the first phase, 6 months later and at the end of the second phase. RESULTS: Mean values of alanine aminotransferase (ALT) showed a clear downward trend and were reduced by 50% at the end of the study while during the first phase these values were similar to basal values (range 32.3-45.5 IU). In the second phase, seroconversion of HBeAg was 56.0% ($p = 0.00001$) and HBV DNA was negative in 36%. The number of patients who showed improvement in Knodell's index was 86.7% in the second phase vs. 13.3% in the first phase ($p = 0.00001$). The drug was well tolerated and the only significant adverse reactions were a reduction in hemoglobin levels greater than 10% of the basal value in 84% of the patients, gastric acidity in 40% and fatigue in 32%. CONCLUSIONS: Ribavirin therapy at a dose of 1,200 mg/day for 24 weeks was well tolerated and efficacious in returning serum ALT levels to normal, in the seroconversion of HBeAg and negativization of HBV DNA as well as in reducing liver necrosis and inflammation. This study confirms that ribavirin may be considered a therapeutic option in the treatment of chronic hepatitis B

Histochemical response of mice to mistletoe lectin I (ML I).

Gossrau R, Franz H.

Histochemistry. 1990; 94(5):531-7.

The acute toxicity of lectin ML I from the toxic drug, mistletoe, was demonstrated in previous experiments. Because the reason for this extremely high toxicity is not yet clear, mice were studied histochemically at different times after treatment with various doses of ML I, ML I A or ML I B chain separately, or recombinations of ML I A and ML I B. Various plasma membrane-associated hydrolases as well as Golgi apparatus- and endoplasmic reticulum-linked hydrolases, peroxisomal and extraperoxisomal oxidases, lysosomal hydrolases, mitochondrial dehydrogenases, the cytoskeletal proteins keratin and vimentin as well as iron, glycogen and lipids were analysed in all organs and tissues of female mice. Irrespective of the dose, a clear-cut response was only observed in the liver. After ML I treatment, glycogen disappeared completely from all hepatocytes, and this effect did not depend on the ML I-concentration and exposure time. The increase in activity of Golgi-associated thiamine pyrophosphatase in hepatocytes and of non-specific alkaline phosphatase in the sinusoidal endothelial cells depended on the applied ML I concentration and the time of treatment. Doses of 600 or 900 ng ML I/kg drastically increased the phosphatase activities. These clear-cut changes of glycogen and enzyme activities were not observed after administration of the ML I B chain alone, and less so when the mice were treated only with the ML I A chain, or were treated with a recombination of ML I A and ML I B even at concentrations higher than that of ML I. (ABSTRACT TRUNCATED AT 250 WORDS)

Prevention of liver cancer.

Guyton KZ, Kensler TW.

Curr Oncol Rep. 2002 Nov; 4(6):464-70.

Hepatocellular carcinoma (HCC) is among the most prevalent and deadly cancers worldwide. Prominent risk factors for HCC include viral hepatitis infection; dietary exposure to hepatotoxic contaminants such as aflatoxins; alcoholism; smoking; and male gender. This review highlights ongoing efforts in HCC prevention. Strategies include vaccination against, and treatment of, viral hepatitis infection. In addition to interferon alpha, an acyclic retinoid (all-trans-3,7,11, 15-tetramethyl-2,4,6,10,14-hexadecapentanoic acid), glycyrrhizin and ginseng are currently under clinical investigation for HCC prevention in Japanese hepatitis C patients. Several recent clinical studies in a Chinese region of pervasive aflatoxin contamination also support the approach of favorably altering aflatoxin metabolism and excretion using the chemopreventive agents oltipraz or chlorophyllin. Agents exhibiting chemopreventive efficacy in preclinical HCC models include vitamins A, D, and E, herbal extracts, a 5alpha-reductase inhibitor, green tea, and D-limonene. Efforts to elucidate the molecular lesions and processes underlying HCC development have identified several putative molecular targets for preventive interventions. These include genes and gene products controlling viral replication, carcinogen metabolism, signal transduction, cell-cycle arrest, apoptosis, proliferation, and oxidative stress

Calcium: effect of different amounts on nonheme- and heme-iron absorption in humans.

Hallberg L, Brune M, Erlandsson M, et al.

Am J Clin Nutr. 1991 Jan; 53(1):112-9.

We investigated the effect of calcium on iron absorption in 126 human subjects. Addition of calcium chloride to wheat rolls significantly reduced iron absorption. Doses between 40 and 600 mg Ca were studied. The inhibition was clearly dose related up to 300 mg Ca. Calcium added to the dough when making the rolls reduced phytate degradation during fermentation and baking. As little as 40 mg Ca added to 80 g flour reduced phytate degradation by 50%, thus increasing the phytate content of the rolls to levels interfering with iron absorption. Calcium also had a direct dose-related inhibiting effect on iron absorption, noted by adding calcium to the rolls after they had been baked instead of to the dough. Iron absorption was reduced by 50-60% at doses of 300-600 mg Ca. Giving 165 mg Ca as milk, cheese, or calcium chloride reduced absorption by 50-60%. The same amount of calcium also significantly reduced heme-iron absorption, suggesting that the effect of calcium is related to the mucosal transfer of iron. The observed marked inhibitory effect on iron absorption of calcium in amounts frequently encountered in normal meals has important nutritional implications

Mistletoe hepatitis.

Harvey J, Colin-Jones DG.

Br Med J (Clin Res Ed). 1981 Jan 17; 282(6259):186-7.

A 49-year-old woman presented with nausea, general malaise, and a dull ache in the right hypochondrium. Liver biopsy showed slight inflammatory-cell infiltration, and results of liver function tests suggested hepatitis. Hepatitis B surface antigen was not detected, and a cholecystogram was normal. Two years later she presented with similar symptoms, and both illnesses were found to have occurred after ingestion of a herbal remedy containing kelp, motherwort, skullcap, and mistletoe. A challenge test established this to be the cause of the illness. Mistletoe is the only constituent of the tablets known to contain any potential toxin and thus was probably the cause of the illness. Mistletoe is widely used in herbal remedies, whose ingestion may therefore cause hepatitis

Risk of needle-stick injuries in the transmission of hepatitis C virus in hospital personnel.

Hernandez ME, Bruguera M, Puyuelo T, et al.

J Hepatol. 1992 Sep; 16(1-2):56-8.

To assess the risk to hospital personnel of acquiring an hepatitis C virus (HCV) infection as a result of occupational exposure to needle-stick injuries, 81 employees who had parenteral exposure to an anti-HCV-positive source were followed for 12 months. None developed hepatitis and anti-HCV testing by a second-generation ELISA system of serum samples collected on the day of exposure and at 3, 6 and 12 months was negative. Consequently, a low efficacy of needle-stick injuries in the transmission of HCV in hospital personnel may be suggested

[Positive effects of essential phospholipids and improvement of life style in patients with toxic liver injury].

Holoman J, Glasa J, Hlavaty I, et al.

Bratisl Lek Listy. 1998 Feb; 99(2):75-81.

Within an open, non-randomized clinical study, the authors investigated the effect of a three-month therapy by a standard product of so-called essential phospholipids in a group of patients (31 men and 2 women, average age being 45.6 +/- 10.8 years) with toxic liver damage--steatosis and steatohepatitis which have developed after exposure to the polychlorinated phenols and cresols, or other potentially toxic chemical substances occurring in working environment and/or exposition to alcohol. The therapy included a recommended change in life routine with a decrease in alcohol consumption, or entire exclusion of alcohol abuse. Within the process of observation, the authors used non-invasive methods (clinical examinations, laboratory examinations, ultrasonographic examination). A special attention was paid to the evaluation of the biotransformation capacity the liver and the assessment of spartein-debrisoquin-dextromethorphan metabolic phenotype. The results of investigation indicated: (1) significant improvement of the subjective status of the treated patients associated with an improvement of ultrasonographic findings of liver steatosis, trend of withdrawal of biochemical activity indices and favourable development of the biotransformation capacity of the liver in a majority of the investigated patients. (2) A very good tolerance of the administered drug without adverse effects. The use of non-invasive surrogate markers in coincidence with clinical investigation of the effect of applied medicamentous therapy in patients with chronic liver diseases represents a methodic increase in current modest options of evaluation of effectively and safety of the new therapeutic procedures in clinical hepato-pharmacology. (Tab. 5, Ref. 42.)

Hepatitis C: the clinical spectrum of disease.

Hoofnagle JH.

Hepatology. 1997 Sep; 26(3 Suppl 1):15S-20S.

Hepatitis C virus (HCV) accounts for approximately 20% of cases of acute hepatitis, 70% of chronic hepatitis, and 30% of end-stage liver disease in the United States. The acute infection has an incubation period of 7 weeks (range, 4-20 weeks) and is symptomatic and icteric in only one third of patients. Serum aminotransferase levels generally increase greater than 10-fold elevated and as symptoms and signs resolve decrease into the normal range. Antibody to HCV is usually but not always present at the time of onset of symptoms. HCV RNA appears in the serum early during the incubation period, increases in titer and peaks at the time of symptoms, and then disappears in resolving disease. Importantly, 85% of patients with acute HCV infection develop chronic infection. In these patients, HCV RNA remains present and in approximately two thirds of patients, aminotransferases remain elevated in the range of 1.5- to 10-fold the upper limit of normal. The course of chronic hepatitis C is variable. Probably fewer than 20% of patients have symptoms and they are usually intermittent, vague, and nonspecific, largely being malaise and easy fatigability. A small percentage of patients develop extrahepatic manifestations of hepatitis C, including cryoglobulinemia and glomerulonephritis. It is estimated that 20% to 30% of patients with chronic hepatitis C develop cirrhosis, but the process is generally slow and insidious. Once cirrhosis develops, symptoms are more common and the signs of end-stage liver disease can appear with jaundice, weakness, wasting, and gastrointestinal bleeding. Patients with cirrhosis are also at risk for developing hepatocellular carcinoma. Thus, this important liver disease has protean manifestations but is often insidious and can lead to end-stage liver disease despite the presence of few symptoms and signs of illness

Lactoferrin markedly inhibits hepatitis C virus infection in cultured human hepatocytes.

Ikeda M, Sugiyama K, Tanaka T, et al.

Biochem Biophys Res Commun. 1998 Apr 17; 245(2):549-53.

We found that bovine lactoferrin (bLF), a milk protein belonging to the iron transporter family, effectively prevented hepatitis C virus (HCV) infection in cultured human hepatocytes (PH5CH8), a cell line susceptible to HCV infection and supportive of HCV replication. Because preincubation of HCV with bLF was required to prevent the infection of HCV to the cells, and preincubation of bLF with the cells showed no inhibitory effect on HCV infection, we demonstrated that the anti-HCV activity of bLF was due to the interaction of bLF with HCV, but not due to the interaction of bLF with the cells. We further found that human lactoferrin also had anti-HCV activity, but bovine transferrin, the other member of the iron transporter family, did not have anti-HCV activity. Our findings suggest that lactoferrin is one of candidates for an anti-HCV reagent that will be well-tolerated and effective in the treatment of patients with chronic hepatitis

Characterization of antiviral activity of lactoferrin against hepatitis C virus infection in human cultured cells.

Ikeda M, Nozaki A, Sugiyama K, et al.

Virus Res. 2000 Jan; 66(1):51-63.

We recently found that bovine lactoferrin (bLF), a milk glycoprotein belonging to the iron transporter family, prevented hepatitis C virus (HCV) infection in human hepatocyte PH5CH8 cells, that are susceptible to HCV infection, and demonstrated that the anti-HCV activity of bLF was due to the interaction of bLF and HCV. In this study we further characterized the anti-HCV activity of

bLF and the mechanism by which bLF prevents HCV infection. We found that bLF inhibited viral entry to the cells by interacting directly with HCV immediately after mixing of bLF and HCV inoculum. The anti-HCV activity of bLF was lost by heating at 65 degrees C, and other milk proteins (mucin, beta-lactoglobulin and casein) did not prevent HCV infection, indicating that bLF prevented HCV infection in a rather specific manner. Furthermore, we found that bovine lactoferricin, a basic N-terminal loop of bLF that is an important region for antibacterial activity, did not exhibit any anti-HCV activity, suggesting that some other region is involved in anti-HCV activity. We confirmed that prevention of HCV infection by bLF was a general phenomenon, because bLF inhibited HCV infection with all five inocula examined, and bLF inhibited HCV infection in human MT-2C T-cells, that were susceptible to HCV infection. In addition, infection with hepatitis G virus, which is distantly related to HCV, was prevented also by bLF. In conclusion, lactoferrin is a natural glycoprotein which effectively protects against HCV infection in hepatocytes and lymphocytes by neutralizing the virus

[Use of a novel hepato-protective preparation "phospholiv" for inhibition of development of chronic hepatitis in rats].

Ipatova OM, Torkhovskaia TI, Kniazhev VA, et al.

Vopr Med Khim. 1998 Nov; 44(6):537-43.

Protective influence of a new phospholipid preparation "Phospholiv" was studied using a model of chronic hepatitis. Animals were treated 45 days intraperitoneally with CCl₄ with parallel intragastral administration of Phospholiv or--(for comparison)--the of other phospholipid hepatoprotector, Essential. Morphologic changes of liver, as well as protein and RNA biosynthesis were evaluated in the end of experiment--by means of measuring C¹⁴-leucine and C¹⁴-orotic acid incorporation into hepatocyte subcellular fractions. Both phospholipid preparations attenuated dystrophic liver changes, Phospholiv effect being more pronounced. They both prevented CCl₄ induced inhibition of label incorporation into subcellular fraction proteins, but only Phospholiv, promoted the maintaining normal level of radioactivity incorporation into cytosol proteins and hepatocyte RNA. The results, confirming certain protective effect of Essential, show more pronounced hepatoprotective action of the new preparation Phospholiv (developed on the basis of polyunsaturated phosphatidylcholine and glycyrrhizinic acid salt). Data show also on possible fit hepatitis treatment

Absence of specific symptoms in chronic hepatitis C.

Iwasaki M, Kanda D, Toyoda M, et al.

J Gastroenterol. 2002; 37(9):709-16.

BACKGROUND: No systematic research has been carried out on the symptoms of chronic hepatitis C, although the disease is believed to induce subjective symptoms such as fatigue or dullness in the legs. **METHODS:** The Todai Health Index has been developed as a symptom checklist that is used for screening particular diseases or for health management. The index was chosen as the most suitable questionnaire for measuring characteristic symptoms of chronic hepatitis C. Sixty patients with chronic hepatitis C who did not have any severe complications were compared with healthy control subjects who were selected randomly from the residents of Iseaki City, Gunma, Japan. **RESULTS:** The major findings were as follows: (1) male and female patients with chronic hepatitis C had no characteristic subjective physical symptoms when compared with the healthy controls, except for a significant difference in aggression, and (2) the severity of the hepatitis was not associated with the patients' symptoms after adjusting for age and treatments. **CONCLUSIONS:** Patients with chronic hepatitis C who did not have any severe complications did not show specific subjective physical symptoms

Oxidative stress in chronic hepatitis C: not just a feature of late stage disease.

Jain SK, Pemberton PW, Smith A, et al.

J Hepatol. 2002 Jun; 36(6):805-11.

BACKGROUND/AIMS: Chronic hepatitis C infection is a major world-wide problem, frequently progressing to cirrhosis, liver failure or hepatoma. The pathological mechanisms of disease progression are unclear but oxidant stress may play a role. **METHODS:** Markers of lipid peroxidation, antioxidant status, hepatic fibrogenesis and liver function were measured in blood or urine from 42 chronic hepatitis C patients. Fibrosis was graded histologically in a subgroup of 33 patients. **RESULTS:** The lipid peroxidation marker 8-isoprostane and the ratio of oxidized to reduced glutathione were significantly elevated ($P < 0.001$, $P = 0.006$). The antioxidants glutathione, selenium and vitamins A, C and E were significantly decreased (all $P < 0.001$) compared to age and sex matched controls. Abnormal values were more marked in cirrhotics, but significant changes were also observed in the non-cirrhotic group. The fibrosis score correlated positively with urinary 8-isoprostane and type III procollagen peptide and negatively with vitamin A. **CONCLUSIONS:** Oxidant stress, as reflected in blood and urine by a wide range of pro- and antioxidant markers, is a significant feature of hepatitis C infection. Although more severe in the cirrhotic group, there was clear evidence of oxidant stress in non-cirrhotic patients. Antioxidant therapy may therefore have a role in slowing disease

progression to cirrhosis

[Viral hepatitis C].

Jankovic S.

Med Pregl. 1999 Nov; 52(11-12):459-63.

INTRODUCTION: Viral hepatitis type C became one of the most dangerous hepatic diseases, bearing high risk of eventually fatal complications. Now a great deal of public health funds has to be used for prevention and treatment of this serious disease. Only very detailed knowledge of the disease could help to a medical practitioner in his everyday confrontation with this serious problem. **MATERIALS AND METHODS:** Data, diagnostic, therapeutic and preventive suggestions given in this paper are result of a comprehensive review of relevant literature. **RESULTS:** The causative agent of hepatitis type C is an RNA virus with six different genotypes. It is easily transmitted from one host to the other only by transferring large amounts of body fluids (blood or plasma transfusion, or prolonged, repeated inoculations of small quantities of infected fluids intravenous drug abusers, recipients of clotting factors, accidental needle sticks). The quantification of the disease activity could be done by a numerical scoring system, originally issued by Knodell, which takes into account four categories: periportal necrosis, intralobular necrosis, portal inflammation and fibrosis. The incubation period of hepatitis C varies from 5 to 7 weeks. It starts like a relatively mild acute disease, but eventually it progresses to chronicity. About 10-20% of patients develops cirrhosis, and yet unknown percentage of patients develops hepatocellular carcinoma. On average, it takes about 30 years for chronic hepatitis C to progress to cirrhosis or cancer. **DISCUSSION:** Serologic testing for anti-HCV proves the existence of specific antibodies against hepatitis C virus. It becomes positive only after 5-6 weeks from clinical onset. Much more sensitive test is PCR, which proves the viral RNA in body fluids. PCR is positive as early as 2 weeks from the onset of hepatitis. Up to now, the only 100% certain way to prove existence of chronic hepatitis is liver biopsy. Interferon alpha is nowadays used for management of this serious disease. The accepted dose is 3,000,000 U three times weekly for 24 weeks. About 46% of treated patients will have both serological and histological improvement. Total liver collagen and iron staining in portal areas are significantly decreased after the treatment course, giving hope for postponing the onset of cirrhosis. However, half of the responders will experience relapse of the disease within 8 months from the end of treatment, and sustained biochemical and virological response could be seen in only 5% of patients. The sustained response rate was increased in some studies to 29% when iron reduction was undertaken along with interferon. **CONCLUSION:** Since there is no effective treatment for hepatitis C, much of the efforts should be directed to prevention. Since hepatitis C virus is transmitted only by parenteral route or close personal contact (sexual contact mostly), in the family environment general hygienic measures are considered sufficient. Hands should be washed properly, food, clothing, utensils, linen and excreta of the patient should be handled separately. During sexual intercourse, prophylactics should be used. The most important measure for prevention of posttransfusion hepatitis C is regular testing of all blood donors for anti-HCV antibodies

Transmission of hepatitis C virus to sexual partners of seropositive patients with bleeding disorders: a rare event.

Kolho E, Naukkarinen R, Ebeling F, et al.

Scand J Infect Dis. 1991; 23(6):667-70.

Sexual transmission of hepatitis C virus (HCV) was studied in 30 partners to anti-HCV positive multitransfused patients with a bleeding disorder. Anti-HCV ELISA C-100 was used as a screening test. Positive results were confirmed with the first generation RIBA test. Indeterminate samples were tested also with the second generation RIBA to verify the positivity. The time of sexual exposure added up was at least 95 years. 29 partners were anti-HCV seronegative. Only 1 partner was anti-HCV indeterminate. Thus sexual transmission of HCV was a rare event

[Chronic hepatitis C].

Kumada H.

Nippon Rinsho. 2002 Jan; 60(1):182-8.

Eleven years have elapsed since the hepatitis type C was first reported and treatment with interferon alone has resulted in about 30% recovery in man. In the case of heavy infection by HCV genotype 1b, 2a, interferon treatment has not been wholly satisfactory and treatment with long term combination of interferon and ribavirin appears to be most effective and a combination of interferon, ribavirin may become the mainstream of the treatment. A duration of one year appears to be most satisfactory. Even when this combination therapy is going, heavy infection by HCV genotype 1b recovery is about 50% and in order to prevent the occurrence of carcinoma, long term treatment with a small dose of interferon must be considered. New agent other than ribavirin must be developed

Long-term treatment of chronic hepatitis C with glycyrrhizin [stronger neo-minophagen C (SNMC)] for preventing liver cirrhosis and hepatocellular carcinoma.

Kumada H.

Oncology. 2002; 62 Suppl 1:94-100.

In Japan, hepatitis C virus (HCV) is the single most frequent cause of hepatocellular carcinoma (HCC), resulting in yearly deaths of over 30,000. Although the mechanism of how HCV induces HCC is not clear, persistent HCV infection and necro-inflammatory changes in chronic hepatitis C accelerate the development of liver cirrhosis and can eventuate in HCC. Hence, means of eradicating HCV as well as suppressing inflammation in the liver, even if patients stay infected with HCV, would decrease the incidence of HCC with chronic hepatitis C. For more than 40 years, a preparation of glycyrrhizin [Stronger Neo-Minophagen C (SNMC)] has been used for the treatment of 'allergic' hepatitis in Japan. In 1977, intravenous injection with SNMC was started in patients with chronic hepatitis or liver cirrhosis, most of whom have turned out to be infected with hepatitis viruses. In a multicenter double-blind study, alanine aminotransferase (ALT) levels decreased in the patients who received 40 ml/day of SNMC for 4 weeks at a rate significantly higher ($p < 0.001$) than controls receiving placebo. Furthermore, SNMC 100 ml/day for 8 weeks improved liver histology in 40 patients with chronic hepatitis, in correlation with improved ALT levels in serum. Liver cirrhosis occurred less frequently in 178 patients on long-term SNMC than in 100 controls (28 vs. 40% at year 13, $p < 0.002$). Finally, HCC developed less frequently in the 84 patients on long-term SNMC than in the 109 controls (13 vs. 25% at year 15, $p < 0.002$). Combined, these results indicate that a long-term treatment with SNMC prevents the development of HCC in the patients with chronic hepatitis. SNMC is particularly helpful in the patients with chronic hepatitis C who fail to respond to interferon and in those who cannot be treated with it for various reasons

Hepatitis C virus infection.

Lauer GM, Walker BD.

N Engl J Med. 2001 Jul 5; 345(1):41-52.

Liver diseases by alcohol and hepatitis C: early detection and new insights in pathogenesis lead to improved treatment.

Lieber CS.

Am J Addict. 2001; 10 Suppl:29-50.

Much progress has been made in the understanding of the pathogenesis of alcoholic liver disease, resulting in improvement of treatment. Therapy must include correction of nutritional deficiencies, while taking into account changes of nutritional requirements. Methionine is normally activated to S-adenosylmethionine (SAME). However, in liver disease, the corresponding enzyme is depressed. The resulting deficiencies can be attenuated by the administration of SAME but not by methionine. Similarly, phosphatidylethanolamine methyltransferase activity is depressed, but the lacking phosphatidylcholine (PC) can be administered as polyenylphosphatidylcholine (PPC). Chronic ethanol consumption increases CYP2E1, resulting in increased generation of toxic acetaldehyde and free radicals, tolerance to ethanol and other drugs, and multiple ethanol-drug interactions. Experimentally, PPC opposes CYP2E1 induction and fibrosis. Alcoholism and hepatitis C infection commonly co-exist, with acceleration of fibrosis, cirrhosis, and hepatocellular carcinoma. PPC is being tested clinically as a corresponding antifibrotic agent. Available antiviral agents are contraindicated in the alcoholic. Anti-inflammatory agents, such as steroids, may be selectively useful. Finally, anticraving agents, such as naltrexone or acamprosate, should be part of therapy

Hepatitis C: transmission by toothbrushes. A myth or a real possibility. *Gastroenterology*.

Lock GDMOF.

Gastroenterology. 2002;(122):A634.

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Broad-spectrum antiviral activity of the IMP dehydrogenase inhibitor VX-497: a comparison with ribavirin and demonstration of antiviral additivity with alpha interferon.

Markland W, McQuaid TJ, Jain J, et al.

Antimicrob Agents Chemother. 2000 Apr; 44(4):859-66.

The enzyme IMP dehydrogenase (IMPDH) catalyzes an essential step in the de novo biosynthesis of guanine nucleotides, namely, the conversion of IMP to XMP. The major event occurring in cells exposed to competitive IMPDH inhibitors such as ribavirin or uncompetitive inhibitors such as mycophenolic acid (MPA) is a depletion of the intracellular GTP and dGTP pools. Ribavirin is approved as an inhaled antiviral agent for treatment of respiratory syncytial virus (RSV) infection and orally, in combination with alpha interferon (IFN-alpha), for the treatment of chronic hepatitis C virus (HCV) infection. VX-497 is a potent, reversible uncompetitive IMPDH inhibitor which is structurally unrelated to other known IMPDH inhibitors. Studies were performed to compare VX-497 and ribavirin in terms of their cytotoxicities and their efficacies against a variety of viruses. They included DNA viruses (hepatitis B virus [HBV], human cytomegalovirus [HCMV], and herpes simplex virus type 1 [HSV-1]) and RNA viruses (respiratory syncytial virus [RSV], parainfluenza-3 virus, bovine viral diarrhea virus, Venezuelan equine encephalomyelitis virus [VEEV], dengue virus, yellow fever virus, coxsackie B3 virus, encephalomyocarditis virus [EMCV], and influenza A virus). VX-497 was 17- to 186-fold more potent than ribavirin against HBV, HCMV, RSV, HSV-1, parainfluenza-3 virus, EMCV, and VEEV infections in cultured cells. The therapeutic index of VX-497 was significantly better than that of ribavirin for HBV and HCMV (14- and 39-fold, respectively). Finally, the antiviral effect of VX-497 in combination with IFN-alpha was compared to that of ribavirin with IFN-alpha in the EMCV replication system. Both VX-497 and ribavirin demonstrated additivity when coapplied with IFN-alpha, with VX-497 again being the more potent in this combination. These data are supportive of the hypothesis that VX-497, like ribavirin, is a broad-spectrum antiviral agent

Response of chronic hepatitis C to interferon-alpha treatment and relationship with iron metabolism.

Martin-Vivaldi R, Noguera F, Gonzalez A, et al.

Rev Esp Enferm Dig. 1997 Jul; 89(7):523-30.

AIM: to prospectively analyze the influence of iron metabolism of the response to interferon-alpha therapy in chronic hepatitis C. METHODS: ninety-two patients with chronic hepatitis C treated with recombinant alpha-interferon were included. Basal serum levels of iron, ferritin and transferrin saturation were compared in responding and nonresponding patients. Additional epidemiologic, histologic and biochemical variables were studied as predictors of response to interferon-alpha therapy. RESULTS: we studied 57 men (62%) and 35 women (35%) with a mean age of 40 years. Biopsy specimens were classified as having chronic active hepatitis (63%), chronic persistent hepatitis (33.8%) or cirrhosis (3.2%). The basal serum levels of iron and ferritin were significantly higher in non responders (126 +/- 9.1 mu/dL and 222.7 +/- 31.9 eta g/dL respectively; $p < 0.05$) than in responders (101 +/- 5.7 micrograms/dL and 136 +/- 24.1 eta g/dL). Mean transferrin saturation was also higher in nonresponders (29.7% +/- 2.7% vs 26% +/- 2.02%) although this difference was not significant. Younger age, absence of cirrhosis and parenteral transmission were associated with an improved response to interferon therapy. No relationship was found between the presence of iron in the hepatic parenchyma and response to interferon treatment. CONCLUSIONS: elevated serum levels of iron, ferritin, or both may be associated with a worse response to interferon-alpha therapy

Interferon alfa 2b alone or in combination with ribavirin as initial treatment for chronic hepatitis.

McHutchinson JGGSCSER.

C N Engl J Med. 1998; 339(21):1485-92.

Hepatitis C virus infection in medical personnel after needlestick accident.

Mitsui T, Iwano K, Masuko K, et al.

Hepatology. 1992 Nov; 16(5):1109-14.

Hepatitis C virus infections in medical personnel after needlestick accidents have been documented generally by detection of seroconversion to a hepatitis C virus nonstructural region antigen, c100-3 (a marker of infection). We tested for hepatitis C virus core-derived antibodies and genomic RNA in addition to c100-3 antibody in 159 cases of needlestick exposure that did not involve patients positive for HBsAg. Of these we found 68 cases with index patients positive for both hepatitis C virus RNA and antibodies and members negative for antibodies to HCV core or c100-3 before the needlestick accidents. Seven of these medical personnel became infected with hepatitis C virus after the accidents. Their hepatitis was generally subclinical or self-limited and transient, except for one patient in whom liver enzyme elevation persisted along with the antibodies. In our study, the risk of hepatitis C virus transmission from a single needlestick accident with hepatitis C virus RNA-positive blood was 10%, considerably higher than the 4% estimated in a previous study. We found that donor blood with antibody to an hepatitis C virus core-derived peptide with enzyme-linked immunosorbent assay optical densities greater than 2.0 carried a significant risk of transmitting hepatitis C virus to needlestick victims. No hepatitis C virus seroconversions occurred in medical personnel exposed to hepatitis C virus antibody-negative or hepatitis C virus RNA-negative blood; however, one such exposure resulted in a very mild non-A, non-B, non-C hepatitis

Pegylation: engineering improved pharmaceuticals for enhanced therapy.

Molineux G.

Cancer Treat Rev. 2002 Apr; 28 Suppl A:13-6.

Conjugating biomolecules with polyethylene glycol (PEG), a process known as pegylation, is now an established method for increasing the circulating half-life of protein and liposomal pharmaceuticals. Polyethylene glycols are nontoxic water-soluble polymers that, owing to their large hydrodynamic volume, create a shield around the pegylated drug, thus protecting it from renal clearance, enzymatic degradation, and recognition by cells of the immune system. Agent-specific pegylation methods have been used in recent years to produce pegylated drugs that have biologic activity that is the same as, or greater than, that of the parent drug. These agents have distinct in vivo pharmacokinetic and pharmacodynamic properties, as exemplified by the self-regulated clearance of pegfilgrastim, the prolonged absorption half-life of pegylated interferon alpha-2a, and the altered tolerability profile of pegylated liposomal doxorubicin. Pegylated agents have dosing schedules that are more convenient and more acceptable to patients, and this can have a beneficial effect on the quality of life of patients with cancer

Oxidative stress in the absence of inflammation in a mouse model for hepatitis C virus-associated hepatocarcinogenesis.

Moriya K, Nakagawa K, Santa T, et al.

Cancer Res. 2001 Jun 1; 61(11):4365-70.

The mechanism of hepatocarcinogenesis in hepatitis C virus (HCV) infection is still undefined. One possibility is the involvement of oxidative stress, which can produce genetic mutations as well as gross chromosomal alterations and contribute to cancer development. We recently showed that after a long period, the core protein of HCV induces hepatocellular carcinoma (HCC) in transgenic mice with marked hepatic steatosis but without inflammation, indicating a direct involvement of HCV in hepatocarcinogenesis. To elucidate the biochemical events before the development of HCC, we examined several parameters of oxidative stress and redox homeostasis in a mouse model of HCV-associated HCC. For young mice ages 3-12 months, there was no significant difference in the levels of hydroperoxides of phosphatidylcholine (PCOOH) and phosphatidylethanolamine in liver tissue homogenates between transgenic and nontransgenic control mice. In contrast, the PCOOH level was increased by 180% in old core gene transgenic mice > 16 months old. Concurrently, there was a significant increase in the catalase activity, and there were decreases in the levels of total and reduced glutathione in the same mice. A direct in situ determination by chemiluminescence revealed an increase in hydroperoxide products by 170% even in young transgenic mice, suggesting that hydroperoxides were overproduced but immediately removed by an activated scavenger system in young mice. Electron microscopy revealed lipofuscin granules, secondary lysosomes carrying various cytoplasmic organelles, and disruption of the double membrane structure of mitochondria, and PCR analysis disclosed a deletion in mitochondrial DNA. Interestingly, alcohol caused a marked increase in the PCOOH level in transgenic mice, suggesting synergism between alcohol and HCV in hepatocarcinogenesis. The HCV core protein thus alters the oxidant/antioxidant state in the liver in the absence of inflammation and may thereby contribute to or facilitate, at least in part, the development of HCC in HCV infection

Pegylated interferon alfa-2b and ribavirin for the treatment of chronic hepatitis C infection in African-Americans and Non-Hispanic whites.

Muir AJBJDKPG.

Gastroenterology. 2002;(122):A630.

Interleukin 10 treatment reduces fibrosis in patients with chronic hepatitis C: a pilot trial of interferon nonresponders.

Nelson DR, Lauwers GY, Lau JY, et al.

Gastroenterology. 2000 Apr; 118(4):655-60.

BACKGROUND & AIMS: Interleukin (IL)-10 is a cytokine that down-regulates the proinflammatory response and has a modulatory effect on hepatic fibrogenesis. The aim of this study was to determine the effect of IL-10 on hepatic injury in patients with chronic hepatitis C. **METHODS:** Twenty-four patients with chronic hepatitis C who had not previously responded to interferon-based therapy were enrolled in a randomized, double-blinded 2-dose trial in which they received either 4 or 8 microgram/kg IL-10 subcutaneously daily for 90 days. Liver biopsies were performed before and at the end of therapy. **RESULTS:** IL-10 was well tolerated with 22 patients completing the study. Serum ALT levels normalized in 19 of 22 patients by the end of therapy and were sustained in 5 of 22. Hepatic inflammation decreased in 19 of 22 patients, with 11 having a

decrease by ≥ 2 . Fibrosis decreased in 14 of 22 patients (mean change, 3.6-2.6; $P = 0.001$). There was no change in serum HCV RNA levels. IL-10 therapy was associated with changes in serological markers, suggesting a reduction of immune response and fibrogenesis. CONCLUSIONS: IL-10 therapy is safe and well tolerated in patients with chronic hepatitis C. Although it has no apparent antiviral activity, IL-10 normalizes serum ALT levels, improves liver histology, and reduces liver fibrosis in a large proportion of patients receiving treatment. Therefore, IL-10 may have therapeutic potential in patients with chronic hepatitis C patients who do not respond to interferon-based therapy

Dilinoleoylphosphatidylcholine selectively modulates lipopolysaccharide-induced Kupffer cell activation.

Oneta CM, Mak KM, Lieber CS.

J Lab Clin Med. 1999 Nov; 134(5):466-70.

Polyenylphosphatidylcholine (PPC), a mixture of polyunsaturated phosphatidylcholines extracted from soybeans, protects against alcoholic and non-alcoholic liver injury. Because Kupffer cells mediate liver injury, we hypothesized that PPC may modulate their activation. The activation of Kupffer cells by lipopolysaccharide (LPS) leads to an enhanced production of cytokines. Among these, tumor necrosis factor- α (TNF- α) exerts mainly a hepatotoxic effect, whereas interleukin-1 β (IL-1 β) appears to be hepatoprotective. The present study evaluated whether dilinoleoylphosphatidylcholine (DLPC), the main component of PPC (40% to 52%), affects LPS-induced Kupffer cell activation in vitro. For comparison, palmitoyl-linoleoylphosphatidylcholine (PLPC), the other major component of PPC (23% to 24%), and distearoylphosphatidylcholine (DSPC), the saturated counterpart of DLPC, were also tested. Rat Kupffer cells were cultured in serum-free RPMI-1640 medium containing 10 micromol/L of either DLPC, PLPC, or DSPC in the presence or absence of LPS (1 microg/mL). After 20 hours in culture, the media were collected for cytokine measurements by enzyme-linked immunosorbent assays. LPS significantly stimulated TNF- α and IL-1 β production by 62% and 328%, respectively. Treatment of Kupffer cells with LPS plus DLPC decreased the production of TNF- α by 23% (12.17 \pm 1.83 pg/ng DNA vs 15.72 \pm 2.74 pg/ng DNA, $P < .05$, $n = 6$) and increased that of IL-1 β by 17% (1.80 \pm 0.16 pg/ng DNA vs 1.54 \pm 0.08 pg/ng DNA, $P < .05$, $n = 6$). No effect of PLPC or DSPC on LPS-induced TNF- α or IL-1 β generation was observed, thereby illustrating the selective effect of DLPC in this process. Thus DLPC selectively modulates the LPS-induced activation of Kupffer cells by decreasing the production of the cytotoxic TNF- α while increasing that of the protective IL-1 β . This dual action of DLPC on cytokines may provide a mechanism for the protective effect against liver injury, but its significance still needs to be determined by in vivo studies

[HCV genotype as a predictor of response to interferon therapy in patients with chronic hepatitis C].

Orito E.

Nippon Rinsho. 2001 Jul; 59(7):1356-62.

Hepatitis C virus (HCV) genotype is one of the most important predicting factors of response to interferon (IFN) therapy in patients with chronic hepatitis C. According to the molecular evolutionary analysis, HCV is classified into six major genotypes. The patients infected with genotype 1 show high HCV RNA levels and poor response to IFN therapy compared to those with genotype 2 or 3. No sufficient data are observed on response to IFN in patients with genotype 4 to 6. When PEG-IFN plus ribavirin therapy is introduced, high proportion of patients without genotype 1 must show complete response. In the near future, to predict good response to IFN therapy, it will be necessary to know whether patients have HCV genotype 1 or not

Different genotypes of hepatitis C virus are associated with different severity of chronic liver disease.

Pozzato G, Kaneko S, Moretti M, et al.

J Med Virol. 1994 Jul; 43(3):291-6.

The presence of the "Japanese type" NS4 region was investigated in two series of patients (53 from Italy and 58 from Japan) with hepatitis C virus (HCV)-related chronic liver disease. The two populations were homogeneous as regard to age, male/female ratio, histological diagnosis, and serum aminotransferase activities. Genomic amplification was carried out by "nested" polymerase chain reaction (PCR) with a pair of primers synthesized according to the sequence of JK-1 isolated in Japan. The presence of viral replication was confirmed further by PCR amplification of the 5'NC region. The NS4 region of the Japanese strain was detected in 24 sera (45%) from Italy and in 44 (71%) from Japan. NS4-positive patients were significantly older and showed an ALT serum level significantly lower ($P < 0.01$) than NS4-negative cases in each group. Cirrhosis was significantly ($P < 0.0007$) more common in NS4-positive than in NS4-negative patients. The HCV genotype was subsequently obtained according to Okamoto. All the NS4-positive patients were infected by Type II, whereas in NS4-negative patients all four genotypes were present though Type II still constituted the majority. Cirrhosis was associated exclusively with Type II both in NS4-positive and -negative subjects. These data indicate that, although the positivity for NS4 "Japanese" region seems to be associated with a more aggressive liver disease, the most prevalent Type II predicts more specifically those who are likely to

Ursodeoxycholic acid and chronic hepatitis C infection.

Puoti C, Pannullo A, Annovazzi G, et al.

Lancet. 1993 May 29; 341(8857):1413-4.

Efficacy and safety of pegylated (40-kd) interferon alpha-2a compared with interferon alpha-2a in noncirrhotic patients with chronic hepatitis C.

Reddy KR, Wright TL, Pockros PJ, et al.

Hepatology. 2001 Feb; 33(2):433-8.

Administration of interferon (IFN) 3 times weekly in patients with chronic hepatitis C (CHC) is associated with low sustained responses, which may be, in part, related to this regimen's inability to maintain IFN concentrations sufficient to suppress viral replication. An enhanced IFN molecule produced by the covalent attachment of a branched 40-kd polyethylene glycol moiety to IFN alpha-2a (PEG[40kd] IFN alpha-2a) exhibits sustained absorption, a restricted volume of distribution, and reduced clearance compared with unmodified IFN alpha-2a. One hundred fifty-nine patients with CHC participated in a randomized, ascending-dose (45 or 90, 180, 270 microg) study comparing PEG(40kd) IFN alpha-2a administered once weekly with 3 MIU IFN alpha-2a administered 3 times weekly for 48 weeks to determine the most appropriate PEG(40kd) IFN alpha-2a dose for subsequent clinical trials. Efficacy was assessed by measuring hepatitis C virus (HCV) RNA following a 24-week treatment-free period. Sustained virological responses for PEG(40kd) IFN alpha-2a once weekly were 10% (45 microg; not significant), 30% (90 microg; $P = .009$), 36% (180 microg; $P = .0006$), and 29% (270 microg; $P = .004$), compared with 3% for the 3-times-weekly 3-MIU IFN alpha-2a regimen. The types and frequencies of adverse events and laboratory abnormalities were similar among all groups. In conclusion, once-weekly PEG(40kd) IFN alpha-2a was associated with a higher number of sustained virological responses compared with IFN alpha-2a 3 times weekly in patients with CHC, but had a similar safety profile. The 180-microg PEG(40kd) IFN alpha-2a dose appeared to be the optimal dose based on sustained virological response and its associated side-effect profile

[Effectiveness of using recombinant interferon alfa2 (reaferon) combined with antioxidants in children with acute hepatitis B].

Reizis AR, Malinovskaia VV, Shekhade S, et al.

Pediatrics. 1992;(1):60-4.

The authors describe the results of the first experience gained with the use of recombinant alpha 2-interferon in children with acute viral hepatitis B. The drug was administered rectally in combination with antioxidants (tocopherol). The study was carried out by the double blind method with randomization and two control groups (given tocopherol alone or placebo alone). 73 children with acute viral hepatitis B were examined. The therapeutic combination reaferon plus tocopherol was established to favour more rapid elimination of dyspeptic and abdominal phenomena, to shorten the time of the liver and spleen size increase, duration of hyperfermentemia, to provide for an accelerated reduction of HBsAg titers, elimination of HBeAg and seroconversion, to stimulate alpha-interferon production by leukocytes, and to activate the system of mononuclear phagocytes

[Clinical aspects and epidemiology of hepatitis C in immunosuppressed children with mostly oncologic diseases].

Rieske K, Domula M, Liebert UG, et al.

Klin Padiatr. 1998 Jul; 210(4):274-8.

Between July and October 1996 hepatitis C virus infection was diagnosed in 21 children who underwent immunosuppressive therapy mainly for malignant diseases. We report on the clinical signs and symptoms, diagnostic procedures and the clinical course of the disease in these patients. Epidemiological, diagnostic and clinical aspects of the outbreak are discussed. Analysis of all available data led to the conclusion that these infections were of nosocomial origin. This requires consequences in the hygienic regimen. In addition to the routinely used antibody-test the HCV-PCR should be the diagnostic method of first choice concerning the HCV-diagnostics in immunocompromised patients

Low rate of HCV transmission from women infected with contaminated anti-D immunoglobulin to their family contacts.

Sachithanandan S, Fielding JF.

Ital J Gastroenterol Hepatol. 1997 Feb; 29(1):47-50.

PURPOSE: To analyse the spread of HCV infection from women infected with batch number proven contaminated anti-D immunoglobulin to their family contacts. **PATIENTS AND METHODS:** Index cases. Sixty women who had been infected with hepatitis C after receiving HCV contaminated anti-D Immunoglobulin. All were positive for HCV antibodies by ELISA (Ortho & Murex, Abbott Laboratories) and RIBA3 (Chiron Corporation, Emerville, California) and were viraemic by PCR for HCV-RNA (Roche Diagnostic Systems, Basel, Switzerland). Liver biopsies were performed in 45 patients. All were in stable longterm relationships. **CONTACTS:** Fifty-five partners and 170 children were tested for HCV antibodies by ELISA (Ortho, Murex). Any positive contact was also tested for antibody by RIBA-3, HCV RNA by PCR, genotype determined and also had a liver biopsy performed. **RESULTS:** No male partners and only one child tested positive for HCV antibodies indicating low exposure over a combined time period of 862 years for partners and 2465 years for children. **CONCLUSIONS:** This study suggests a zero female to male sexual transmission rate of HCV and a low vertical transmission rate in anti-D associated HCV infection

New treatment strategies in non-responder patients with chronic hepatitis C.

Schalm SW, Brouwer JT, Bekkering FC, et al.

J Hepatol. 1999; 31 Suppl 1:184-8.

There is solid evidence that retreatment of non-responders with standard regimens of interferon monotherapy is of no clinical value. On the other hand, combination therapy with interferon and ribavirin now produces sustained response rates in non-responders similar to those of interferon monotherapy in untreated patients. Consequently, retreatment of non-responders with the combination of interferon-ribavirin appears to be a valid treatment option. The efficacy of retreatment with the interferon-ribavirin combination can probably be increased by modifying the first weeks of interferon therapy from standard (3 MU tiw) to induction (10 MU daily), and by extending the treatment period to 12 months. In the next few years, the additive value of amantadine to interferon or to interferon-ribavirin combination in inducing sustained viral clearance should be explored. For the many patients who still do not respond with viral clearance despite these new approaches, the goal of therapy might be shifted towards persistent ALT normalization in order to reduce the progression of liver disease. Drugs that can normalize serum ALT such as interferon, ursodeoxycholic acid, ribavirin and glycyrrhizin should be evaluated for this objective

Advances in treatment of chronic hepatitis C: 'pegylated' interferons.

Sharieff KA, Duncan D, Younossi Z.

Cleve Clin J Med. 2002 Feb; 69(2):155-9.

New regimens consisting of pegylated interferons plus ribavirin may produce a sustained virologic response in more than 50% of cases of chronic hepatitis C. In contrast, the combination of standard interferon alfa and ribavirin, which was the standard of care until recently, produced a sustained virologic response in 35% to 40% of cases. As the efficacy of newer regimens improves, additional steps to adequately manage their side effects and maximize adherence may become crucial

Chronic hepatitis C: implications for the primary care clinician.

Smith JR, Herrera JL.

JAAPA. 2001 Feb; 14(2):41-4, 63.

The seeds of an epidemic were sown 2 decades ago, and PAs need to be alert for those at risk for developing chronic hepatitis C before cirrhosis, liver failure, or liver cancer develops. Identifying the patient at risk is as uncomplicated as asking the right questions in the right setting

[Mechanism of action of silibinin. V. Effect of silibinin on the synthesis of ribosomal RNA, mRNA and tRNA in rat liver in vivo].

Sonnenbichler J, Zetl I.

Hoppe Seylers Z Physiol Chem. 1984 May; 365(5):555-66.

The influence of the flavonolignane Silibinin on the rate of RNA synthesis in rat livers was studied in detail and the time course of the stimulatory effect was determined: 8 h after i.p. application a maximal increase of about 60% in nuclear RNA synthesis can

be observed. The analysis of the RNA by electrophoresis on agarose and by sucrose gradient centrifugation demonstrated that in particular the ribosomal RNA (28S, 18S, 5.8S) synthesis is accelerated followed by enhanced incorporation of rRNA into mature ribosomes. During stimulation also changes in the pattern of 45S RNA can be observed. The synthesis of mRNAs, 5S RNA and tRNAs is not influenced by Silibinin, which was shown after separation of these moieties on oligo(dT)-cellulose, and by polyacrylamid electrophoresis, respectively. The clinically observed enhancement of liver cell regeneration during Silibinin treatment thus can be explained by an increase of the protein synthetic apparatus

Stimulatory effect of Silibinin on the DNA synthesis in partially hepatectomized rat livers: non-response in hepatoma and other malign cell lines.

Sonnenbichler J, Goldberg M, Hane L, et al.

Biochem Pharmacol. 1986 Feb 1; 35(3):538-41.

Biochemical effects of the flavonolignane silibinin on RNA, protein and DNA synthesis in rat livers.

Sonnenbichler J, Zetl I.

Prog Clin Biol Res. 1986; 213:319-31.

Serum thioredoxin elucidates the significance of serum ferritin as a marker of oxidative stress in chronic liver diseases.

Sumida Y, Nakashima T, Yoh T, et al.

Liver. 2001 Oct; 21(5):295-9.

BACKGROUND/AIMS: Serum thioredoxin (TRX) levels have recently been established as an indicator of oxidative stress in various diseases. The aim of the present study was to clarify the clinical significance of serum ferritin in chronic liver diseases. **METHODS:** Levels of ferritin, transferrin saturation (TS), aspartate aminotransferase (AST), and TRX were measured in the sera of patients with chronic hepatitis C (CH-C, n=92), chronic hepatitis B (CH-B, n=28), nonalcoholic fatty liver (FL, n=31), or alcoholic liver diseases (ALD, n=17). Serum TRX levels were evaluated with a recently established sandwich enzyme-linked immunosorbent assay kit. **RESULTS:** Serum TRX levels were significantly higher in CH-C, FL, and ALD than in healthy volunteers. A larger proportion of patients with CH-C, FL, and ALD had elevated levels of serum ferritin than CH-B. Serum ferritin levels were positively correlated with levels of TS, AST, and TRX in CH-C, but were merely correlated with TS values in CH-B. Ferritin levels were also well correlated with AST and TRX, but not with TS in FL and ALD. **CONCLUSION:** Oxidative stress, which was evaluated by measuring serum TRX, in addition to storage iron and hepatocyte damage is a cause of increasing serum ferritin levels in chronic liver diseases. An elevated serum ferritin level, which was correlated with TS, indicates that iron-induced oxidative stress contributes to CH-C. Elevated ferritin levels in FL and ALD may be mostly due to iron-unrelated stresses

Absence of nonpercutaneous transmission of hepatitis C virus in a colony of chimpanzees.

Suzuki E, Kaneko S, Uono T, et al.

J Med Virol. 1993 Apr; 39(4):286-91.

Transmission of hepatitis C virus (HCV) was studied in a colony of 85 chimpanzees using assays for anti-HCV and HCV-RNA. Thirteen of the 85 sera were positive for anti-HCV, and 12 of the 13 were also positive for HCV-RNA. All of the anti-HCV positive sera except one were obtained from chimpanzees which had been inoculated with non-A, non-B hepatitis virus. On the other hand, only one of 63 sera of chimpanzees without history of experimental infection of the virus was positive for anti-HCV. Transmission to this chimpanzee was thought to be a needle contaminated with HCV. All 39 samples of chimpanzees born in the center were negative for both anti-HCV and HCV-RNA. Sixteen of their mothers had undergone experimental infection, and 6 of them were positive for both anti-HCV and HCV-RNA. These results suggest that nonpercutaneous transmission, including sexual and mother-to-infant transmissions, is not an important mode of transmission. If these findings apply to humans, definition of inapparent sources of the infection is needed

The role of folic acid in deficiency states and prevention of disease.

Swain RA, St Clair L.

J Fam Pract. 1997 Feb; 44(2):138-44.

Folic acid, a water-soluble vitamin, has been used since the 1940s to treat some cases of macrocytic anemia without neurologic disease. Folate deficiency is best diagnosed with red blood cell folate levels along with macrocytosis and/or megaloblastic anemia. In addition to reversing overt deficiency, the vitamin may reduce the incidence of neural tube defects by 45% in women who receive 400 micrograms per day. It is recommended that all women of childbearing age take 400 micrograms of folate per day. Elevations in homocysteine levels, a metabolite intimately associated with folate, are also being found with increasing regularity in those with cardiovascular diseases. Homocysteine levels are reduced by folic acid administration. Therefore, there is some biologic plausibility, but not currently direct proof, for the assumption that folate supplements may prevent heart disease, stroke, and peripheral arterial disease. Controlled trials should take place before widespread food supplementation with folate is carried out on a large scale because of the possibility of outbreaks of permanent B12-related neurologic damage in those with undiagnosed pernicious anemia. However, if a patient has a premature cardiovascular event and has minimal risk factors, ordering a test to determine homocysteine level may be advisable, and if elevated, treating with folic acid supplement as long as B12 deficiency does not coexist

[Diagnosis of B and C viral hepatitis: new developments and relevance for general practice].

Tappe U, Muller R.

Schweiz Rundsch Med Prax. 2002 May 29; 91(22):964-9.

Diagnosis of hepatitis B and hepatitis C viral infections can be achieved by highly specific and sensitive primary serological screening assays. Still more costly amplification systems on the qualitative and quantitative detection of HBV-DNA and HCV-RNA are only used for answering special clinical questions. They are relevant to indicate antiviral therapy or to control the outcome of treatment. They are rarely necessary for diagnostic purposes as it may happen in immunosuppressed persons. While in hepatitis B activities of aminotransferases and liver histology usually present a good correlation this is not dependably seen in hepatitis C. Histologic evaluation still appears the only reliable diagnostic procedure for determining inflammatory activity and fibrosis progression in hepatitis C. Liver biopsy therefore is considered mandatory prior to initiation of treatment especially since only patients suffering from severe disease with progression to liver cirrhosis may benefit from today's standard treatment procedures

Hepatitis C. Epidemiologic quandaries.

Thomas DL.

Clin Liver Dis. 2001 Nov; 5(4):955-68.

Although many aspects of the transmission of HCV have been clarified, some important issues remain controversial, and the conventional wisdom may be based more on opinion than data (Table 2). HCV is transmitted by percutaneous exposure to contaminated blood, uncommonly from a mother to her infant and between sexual partners, and rarely during the provision of medical care in developed nations. Improved behavioral research instruments are needed to further the understanding of the practices that actually transmit infection. In addition, large, prospective studies are necessary to characterize the frequency [table: see text] of transmission between sexual partners and the potential role of cesarian section in reducing HCV transmission to infants

Effect of iron depletion on long-term response to interferon-alpha in patients with chronic hepatitis C who previously did not respond to interferon therapy.

Tsai NC, Zuckerman E, Han SH, et al.

Am J Gastroenterol. 1997 Oct; 92(10):1831-4.

About half of patients with chronic hepatitis C treated with interferon will not have a biochemical or virological response. Several studies suggested that increased hepatic iron content may negatively influence the response to interferon. We conducted this prospective trial to evaluate the effect of iron depletion on the response to a repeat course of interferon in 20 chronic hepatitis C patients who previously had not responded to interferon. The patients underwent 500-ml phlebotomies every 2 weeks until iron deficiency was achieved. Patients were then started on a 6-month course of interferon alfa-2b (3 million units, t.i.w.). These patients required a mean of 6.0 (range, 1-14) phlebotomies to become iron deficient. ALT levels decreased in 18 of 20 patients and became normal in 4 patients. Mean ALT levels decreased from 154.2 to 87.9 U/L ($p = 0.0006$). At the end of 24 wk of interferon therapy, ALT levels were normal in 11 patients, 3 of whom had undetectable HCV RNA in the serum. One additional patient with abnormal ALT had undetectable HCV RNA. After 6 months of follow-up, one of the HCV RNA negative patients relapsed with reappearance of HCV RNA and elevation of ALT. In summary, 15% of chronic hepatitis C patients who previously

failed interferon now had a sustained response to interferon therapy that was preceded by iron depletion

Combined ursodeoxycholic acid and glycyrrhizin therapy for chronic hepatitis C virus infection: a randomized controlled trial in 170 patients.

Tsubota A, Kumada H, Arase Y, et al.

Eur J Gastroenterol Hepatol. 1999 Oct; 11(10):1077-83.

OBJECTIVE AND DESIGN: To assess the efficacy and safety of combination therapy using ursodeoxycholic acid with glycyrrhizin for chronic hepatitis C virus infection, we conducted a prospective randomized controlled trial of glycyrrhizin (group G) compared with glycyrrhizin plus ursodeoxycholic acid (group G+U) in 170 patients. **METHODS:** All patients had elevated serum aminotransferase levels over 6 months before entry into the trial. Glycyrrhizin was administered to both groups for 24 weeks, and in group G+U, ursodeoxycholic acid (600 mg/day) was administered orally as well. **RESULTS:** Serum aspartate transaminase and alanine transaminase concentrations significantly decreased during treatment in both groups, but serum gamma-glutamyl transpeptidase concentrations fell significantly only in group G+U. Concentrations of all three enzymes fell significantly more in group G+U than in group G, and had normalized in more cases when the trial ended at 24 weeks. However, levels of HCV viraemia did not change during the trial in either group. Multiple regression analysis linked only the treatment regimen, not HCV-related factors or liver histology, to the degree of serum enzyme reduction. No adverse effects were noted in either group. **CONCLUSIONS:** The combined therapy with ursodeoxycholic acid and glycyrrhizin is safe and effective in improving liver-specific enzyme abnormalities, and may be an alternative to interferon in chronic hepatitis C virus infection, especially for interferon-resistant or unstable patients

Biochemical bases of the pharmacological action of the flavonoid silymarin and of its structural isomer silibinin.

Valenzuela A, Garrido A.

Biol Res. 1994; 27(2):105-12.

The flavonoid silymarin and one its structural components, silibinin, have been well characterized as hepato-protective substances. However, little is known about the biochemical mechanisms of action of these substances. This review deals with recent investigations to elucidate the molecular action of the flavonoid. Three levels of action have been proposed for silymarin in experimental animals: a) as an antioxidant, by scavenging prooxidant free radicals and by increasing the intracellular concentration of the tripeptide glutathione; b) regulatory action of the cellular membrane permeability and increase of its stability against xenobiotic injury; c) at the nuclear expression, by increasing the synthesis of ribosomal RNA by stimulating DNA polymerase I and by exerting a steroid-like regulatory action on DNA transcription. The specific hepatoprotective action of silibinin against the toxicity of ethanol, phenylhydrazine and acetaminophen is also discussed. It is suggested that the biochemical effects observed for the flavonoid in experimental models may settle the basis for understanding the pharmacological action of silymarin and silibinin

Combination therapy for chronic hepatitis C: interferon and ribavirin. Preliminary results of individual therapy of chronic hepatitis C by Ukraine and interferon-alpha.

Voltchek ISTNJWGT.

Drugs Exp Clin Res. 2000; 26(5-6):261-6.

Hepatic uptake and antihepatotoxic properties of vitamin E and liposomes in the mouse.

Werner C, Wendel A.

Chem Biol Interact. 1990; 75(1):83-92.

Intravenous administration of soybean phosphatidylcholine liposomes containing different amounts of tocopherol acetate leads to a dose and time dependent increase of mouse liver tocopherol content, which was not observed when the preparation was given orally. When benzo[a]pyrene pretreated mice intoxicated with 400 mg/kg AAP were pretreated 2 h before with 1 g/kg phosphatidylcholine liposomes containing 4 mg/kg vitamin E acetate, these animals were protected against liver damage. Vitamin E alone or liposomes lacking vitamin E showed no protection. In an inflammatory liver disease model, i.e. fulminant hepatitis induced by intraperitoneal administration of 700 mg/kg galactosamine and 1 microgram/kg lipopolysaccharide phosphatidylcholine liposomes protected at a dose of 1 g/kg i.v. In this case, however, the protection was not due to the presence of vitamin E. These findings demonstrate the usefulness of phosphatidylcholine for liver protection and show that the

protective spectrum is improved when they contain vitamin E. The data suggest that phosphatidylcholine is an excellent carrier for delivery of vitamin E to the liver

Hepatitis C virus envelope proteins bind lactoferrin.

Yi M, Kaneko S, Yu DY, et al.

J Virol. 1997 Aug; 71(8):5997-6002.

Hepatitis C virus (HCV) has two envelope proteins, E1 and E2, which form a heterooligomer. During dissection of interacting regions of HCV E1 and E2, we found the presence of an interfering compound or compounds in skim milk. Here we report that human as well as bovine lactoferrin, a multifunctional immunomodulator, binds two HCV envelope proteins. As determined by far-Western blotting, the bacterially expressed E1 and E2 could bind lactoferrin in human milk directly separated or immunopurified and separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The bindings of lactoferrin and HCV envelope proteins in vitro were confirmed by another method, the pull-down assay, with immunoprecipitated lactoferrin-bound protein A resin. By the same assay, mammal-expressed recombinant E1 and E2 were also demonstrated to bind human lactoferrin efficiently in vitro. Direct interaction between E2 and lactoferrin was proved in vivo, since anti-human lactoferrin antibody efficiently coimmunoprecipitated with secreted and intracellular forms of the E2 protein, but not glutathione S-transferase (GST), from lysates of HepG2 cells transiently cotransfected with the expression plasmids of human lactoferrin and gE2t-GST (the N-terminal two-thirds of E2 fused to GST) or GST. The N-terminal loop of lactoferrin, the region important for the antibacterial activity, has only a little role in the binding ability to HCV E2 but affected the secretion or stability of lactoferrin. Taken together, these results indicate the specific interaction between lactoferrin and HCV envelope proteins in vivo and in vitro

The roles of amantadine, rimantadine, ursodeoxycholic acid, and NSAIDs, alone or in combination with alpha interferons, in the treatment of chronic hepatitis C.

Younossi ZM, Perrillo RP.

Semin Liver Dis. 1999; 19 Suppl 1:95-102.

Although alpha interferons are currently the standard treatments for chronic hepatitis C, they are effective in only 15% to 20% of patients. This low success rate has prompted research into new approaches for maximizing responses to alpha interferons. A variety of drugs have been investigated alone or in combination with alpha interferons. Of these agents, ribavirin is currently the most promising adjuvant, and the combination therapy of ribavirin plus recombinant interferon alfa-2b is reviewed in detail elsewhere in this issue (see Davis article, pp. 49-55; and McHutchison article, pp. 57-65). This article reviews the literature concerning studies of amantadine, rimantadine, ursodeoxycholic acid (UDCA), and nonsteroidal anti-inflammatory drugs (NSAIDs), which are the most commonly used alternatives to ribavirin. As of this writing, virologic response rates have been unsatisfactory when these agents are used as monotherapies. Furthermore, combining alpha interferons with either UDCA or NSAIDs does not appear to improve sustained virologic response rates. However, combination regimens composed of an alpha interferon plus amantadine, or an alpha interferon plus rimantadine, or triple therapy with either amantadine or rimantadine plus an alpha interferon and ribavirin, warrant further investigation

Protective role of selenium against hepatitis B virus and primary liver cancer in Qidong.

Yu SY, Zhu YJ, Li WG.

Biol Trace Elem Res. 1997 Jan; 56(1):117-24.

High rates of hepatitis B virus (HBV) infection and primary liver cancer (PLC) are present in Qidong county. Epidemiological surveys demonstrated an inverse association between selenium (Se) level and regional cancer incidence, as well as HBV infection. Four-year animal studies showed that dietary supplement of Se reduced the HBV infection by 77.2% and liver precancerous lesion by 75.8% of ducks, caused by exposure to natural environmental etiologic factors. An intervention trial was undertaken among the general population of 130,471. Individuals in five townships were involved for observation of the preventive effect of Se. The 8-yr follow-up data showed reduced PLC incidence by 35.1% in selenized table salt supplemented vs the nonsupplemented population. On withdrawal of Se from the treated group, PLC incidence rate began to increase. However, the inhibitory response to HBV was sustained during the 3-yr cessation of treatment. The clinical study among 226 Hepatitis B Surface Antigen (HBsAg)-positive persons provided either 200 micrograms of Se in the form of selenized yeast tablet or an identical placebo of yeast tablet daily for 4 yr showed that 7 of 113 subjects were diagnosed as having PLC in the placebo group, whereas no incidence of PLC was found in 113 subjects supplemented with Se. Again on cessation of treatment, PLC developed at a rate comparable to that in the control group, demonstrating that a continuous intake of Se is essential to sustain the chemopreventive effect

Activity of HDV ribozymes to trans-cleave HCV RNA.

Yu YC, Mao Q, Gu CH, et al.

World J Gastroenterol. 2002 Aug; 8(4):694-8.

AIM: To explore whether HDV ribozymes have the ability to trans-cleave HCV RNA. **METHODS:** Three HDV genomic ribozymes were designed and named RzC1, RzC2 and RzC3. The substrate RNA contained HCV RNA 5'-noncoding region and 5'-fragment of C region (5'-NCR-C). All the ribozymes and HCV RNA 5'-NCR-C were obtained by transcription in vitro from their DNA templates, and HCV RNA 5'-NCR-C was radiolabelled at its 5'-end. Under certain pH, temperature, appropriate concentration of Mg(2+) and deionized formamide, these ribozymes were respectively or simultaneously mixed with HCV RNA 5'-NCR-C and reacted for a certain time. The trans-cleavage reaction was stopped at different time points, and the products were separated with polyacrylamide gel electrophoresis (PAGE), displayed by autoradiography. Percentage of trans-cleaved products was measured to indicate the activity of HDV ribozymes. **RESULTS:** RzC1 and RzC2 could trans-cleave 26 % and 21.8 % of HCV RNA 5'-NCR-C under our reaction conditions with 2.5 mol.L(-1) deionized formamide respectively. The percentage of HCV RNA 5'-NCR-C trans-cleaved by RzC1, RzC2 or combined usage of the three ribozymes increased with time, up to 24.9 %, 20.3 % and 37.3 % respectively at 90 min point. Almost no product from RzC3 was observed. **CONCLUSION:** HDV ribozymes are able to trans-cleave specifically HCV RNA at certain sites under appropriate conditions, and combination of several ribozymes aiming at different target sites can trans-cleave the substrate more efficiently than using only one of them

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