

Hepatitis B

ABSTRACTS

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Thymosin alpha-1.

Ancell CD, Phipps J, Young L. Nova Factor, Memphis, TN, USA.

Am J Health Syst Pharm. 2001 May 15;58(10):879-85; quiz 886-8.

The pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of thymosin alpha-1 (TA1) are reviewed. TA1 is a synthetic polypeptide. The drug is in Phase III trials for the treatment of hepatitis C and in Phase II trials for hepatitis B. Additional possible indications are malignant melanoma, hepatocellular carcinoma, drug-resistant tuberculosis, and DiGeorge's syndrome. TA1 is thought to modulate the immune system by augmenting T-cell function. TA1 may affect thymocytes by stimulating their differentiation or by converting them to active T cells. TA1 is rapidly absorbed, achieving peak serum concentrations within two hours. Blood levels return to baseline within 24 hours, and the serum half-life is approximately 2 hours. TA1's efficacy in hepatitis B has been evaluated in 195 patients in four clinical trials. One study found hepatitis B virus (HBV) DNA clearance at six months in 9 of 17 patients receiving TA1, compared with 10 of 16 patients treated with interferon alfa-2b (IFN-alpha 2b) and 4 of 15 historical controls. An open-label trial found HBV DNA clearance in 53% of patients at six months. A randomized, controlled trial found HBV DNA clearance in 40.6% and 25.6% of patients treated with TA1 for 6 and 12 months, respectively, compared with 9.4% of untreated controls. Efficacy for hepatitis C has been evaluated in 162 patients in three clinical trials. In one trial, the number of patients who achieved normal serum alanine aminotransferase (ALT) levels did not differ significantly between TA1 and placebo. In the other two trials, combination TA1 and IFN-alpha 2b was compared with IFN-alpha 2b alone. One trial found a normal serum ALT level at six months in 71% of patients receiving combination therapy, versus 35% of patients receiving IFN-alpha 2b alone. Hepatitis C virus RNA clearance occurred in 65% of patients treated with combination therapy and 29% of patients treated with IFN-alpha 2b alone. The third trial, comparing combination TA1 and IFN-alpha 2b with IFN-alpha 2b alone and with placebo, found normalization of ALT levels at six months in 37.1% of patients receiving combination therapy, 16.2% of patients receiving IFN-alpha 2b alone, and 2.7% of patients receiving placebo. TA1 is well tolerated. Most studies observed only local irritation at the injection site. For hepatitis B and C, TA1 1.6 mg (900 micrograms/m²) should be administered subcutaneously twice a week. Clinical trials of TA1 for chronic hepatitis B or C have had mixed results. TA1 may be useful as monotherapy for hepatitis B or in combination with IFN-alpha 2b for hepatitis C, but its effects on morbidity and mortality remain to be seen.

A comparative trial of standard or high-dose S subunit recombinant hepatitis B vaccine versus a vaccine containing S subunit, pre-S1, and pre-S2 particles for revaccination of healthy adult nonresponders.

Bertino JS Jr, Tirrell P, Greenberg RN, Keyserling HL, Poland GA, Gump D, Kumar ML, Ramsey K. Bassett Healthcare, Cooperstown, New York 13326-1394, USA.

J Infect Dis. 1997 Mar;175(3):678-81.

The efficacy of 10-microg and 40-microg hepatitis B vaccines was compared with that of an investigational vaccine containing pre-S1, pre-S2, and S subunit particles (mixed particle vaccine) in inducing protective anti-hepatitis B surface antigen (anti-HBs) concentrations in 46 otherwise healthy persons who previously did not develop measurable levels of antibodies to at least one complete course of vaccine. A statistically significant difference was seen in the percentage of subjects who developed protective levels of anti-HBs (> or = 10 mIU/mL) with three 40-microg doses of S subunit vaccine versus the other groups. One hundred percent of the 40-microg dose group developed protective anti-HBs titers. No difference in adverse effects was noted.

Resistance of hepatitis B virus to antiviral drugs: current aspects and directions for future investigation.

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Antivir Chem Chemother. 2001 Jan;12(1):1-35.

Despite the existence of vaccines, chronic hepatitis B virus (HBV) infection remains a major health problem worldwide. Interferon therapy successfully controls infection in only a small percentage of chronically infected individuals. The recent approval of the nucleoside analogue lamivudine for the treatment of chronic HBV infection has ushered in a new era of antiviral therapy. While lamivudine is highly effective at controlling viral infection short-term, prolonged therapy has been associated with an increasing incidence of viral resistance. Thus, it appears that lamivudine alone will not be sufficient to control chronic viral infection in the majority of individuals. In addition to lamivudine, several new nucleoside and nucleotide analogues that show promising

antihepadnaviral activity are in various stages of development. Lamivudine resistance has been found to confer cross-resistance to some of these compounds and it is likely that resistance to newer antivirals may also develop during prolonged use. Drug resistance therefore poses a major threat to nucleoside analogue-based therapies for chronic HBV infection. Fortunately, combination chemotherapy (antiviral therapy with two or more agents) can minimize the chance that resistance will develop and can be expected to achieve sustained reductions in viral load, provided that suitable combinations of agents are chosen. Here we review the basis of drug resistance in HBV, with emphasis on aspects that are likely to affect drug choice in future.

Nonresponders to hepatitis B vaccine can present envelope particles to T lymphocytes.

Desombere I, Hauser P, Rossau R, Paradijs J, Leroux-Roels G. Department of Clinical Chemistry, University of Ghent, Belgium.

J Immunol. 1995 Jan 15;154(2):520-9.

The mechanisms causing nonresponsiveness to hepatitis B surface Ag (HBsAg) vaccines in humans remain largely unknown. The increased incidence of nonresponsiveness in subjects with HLA-DR3 or -DR7 haplotype suggests that immune response mechanisms governed by genes of the MHC are involved. It is conceivable that APC of nonresponders are defective in the presentation of HBsAg because they are unable to adequately take up, process, or present this Ag. To examine this hypothesis we have used PBMC from nonresponders to present recombinant particles containing S or PreS2-S sequences to HBsAg-specific T cell lines from haplo-identical responder vaccinees. The proliferative response of these lines was used to evaluate the efficacy of Ag presentation. Unfractionated PBMC from five DR2+ and six DR7+ nonresponders did not proliferate to HBsAg in vitro, whereas they vigorously proliferated upon stimulation with tetanus toxoid, thus ruling out the presence of a generalized immunodeficiency. All DR2 (15)+ nonresponders were able to present hepatitis B envelope Ag to HBsAg-specific, DR1501-restricted T cells. PBMC from six DR7+ nonresponders were all able to present HBsAg to DR07-restricted T cell lines and PBMC from three DPw4+ nonresponders were able to present HBsAg to DP0402-restricted T cell lines. Additional experiments showed that PBMC from two nonresponders presented HBsAg equally well and sometimes better than PBMC from two partially HLA-matched high responders. We conclude that HLA-DR2+, -DR7+, and -DPw4+ nonresponder vaccinees are able to take up, process and present HBsAg to allogeneic, haplo-identical T cell lines in vitro.

HLA tissue types in nonresponders to hepatitis B vaccine.

Durupinar B, Okten G. Department of Microbiology and Clinical Microbiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkiye.

Indian J Pediatr. 1996 May-Jun;63(3):369-73.

Genetic factors are implicated in the response of normal subjects to hepatitis B vaccine. In order to investigate the immunogenetic factors associated with nonresponsiveness to hepatitis B vaccine, 93 health care workers were vaccinated with hepatitis B vaccine. Initial nonresponders (antibody not detected or antibody detected but < 10 mIU/ml) were revaccinated. Only 12 (12.9%) of the 93 health care workers, who had anti-HBs levels of 10 mIU/ml or less after revaccination were defined as absolute nonresponders. HLA typing were performed in these 12 nonresponders, Anti-HBs levels were determined by ELISA method in mIU/ml units. HLA-A,B,C,DR, and DQ typing was performed using the microcytotoxicity test. The HLA-A10 (pc less than 0.01) and CW4 (pc less than 0.006) were decreased whereas DR7 (pc less than 0.09) was increased in nonresponders. Although our initial results suggest the importance of genetic modulation of responsiveness to hepatitis B vaccine, a formal demonstration of the mode of inheritance of unresponsiveness to hepatitis B vaccine and the explanation of the role of genes in this matter will require further studies of families.

Current pharmacotherapy for hepatitis B infection.

Galan MV, Boyce D, Gordon SC. Division of Gastroenterology-Hepatology, William Beaumont Hospital, Royal Oak, Michigan 48073, USA.

Expert Opin Pharmacother. 2001 Aug;2(8):1289-98.

Chronic infection with the hepatitis B virus (HBV) affects 350 million people worldwide, or approximately 5% of the global population, and commonly results in cirrhosis and hepatocellular carcinoma. Until recently, the only available treatment was injectable interferon alpha and response rates were suboptimal. Moreover, this expensive and toxic therapy had little applicability in the endemic regions of the world, i.e., Asia and Africa. The realisation that orally available nucleoside and nucleotide agents may effectively control this infection opened a new era in the management of chronic hepatitis B. Oral lamivudine recently became approved for treatment of hepatitis B worldwide. It is free of significant toxicity, improves liver histology and rapidly diminishes HBV DNA levels; lamivudine is expected to become the first-line therapy of choice. Nevertheless, the consistent emergence of lamivudine-resistant variants mandates the need to develop additional therapeutic agents. Adefovir dipivoxil, a nucleotide, and entecavir, a nucleoside agent, are promising new drugs that might eventually be used in combination with lamivudine and therefore reduce the incidence of drug resistance. There is a critical need to advance the research of hepatitis B antiviral agents so that

effective combination therapies can become widely available.

Advances in antiviral agents for hepatitis B virus.

Gumina G, Song GY, Chu CK. Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, University of Georgia, Athens.

Antivir Chem Chemother. 2001;12 Suppl 1:93-117.

Hepatitis B virus (HBV) is the third most common disease after venereal diseases and chickenpox. HBV currently infects 2 billion people in the world, of which 350 million are chronic carriers. At least 1 million chronically infected individuals die each year due to HBV-related diseases, especially cirrhosis and liver cancer. The greatest concern about the diffusion of this virus is in endemic regions in central and southern Africa, South-East Asia and South America, where neonatal exposure results in high mortality rates. Anti-HBV therapy has made important progresses in the last decade, with two approved drugs and a number of other potent agents in the pharmaceutical industry pipeline. Nevertheless, resistance and viral rebound are still major issues in devising a winning strategy, and there is a continuous need of developing new active compounds, as well as therapeutic protocols based on combination therapy and a prophylactic approach. This review will summarize the latest advances in anti-HBV therapy, with particular regard to the latest clinical data on the most significant anti-HBV agents. Issues such as viral resistance and combination therapy will be highlighted.

[Clinical aspects and therapy of viral hepatitis] [Article in German]

Lammert F, Busch N, Matern S. Medizinische Klinik III, Universitätsklinikum der RWTH Aachen.

Chirurg. 2000 Apr;71(4):381-8.

Acute hepatitis can be caused by the enterically spread hepatitis A and E viruses and the parenterally spread hepatitis B, C or D viruses. The clinical features of acute viral hepatitis are similar among the five viruses and include non-specific symptoms and icterus. In general, a specific therapy is not necessary, but patients with fulminant hepatitis may require liver transplantation. For acute hepatitis C, the effect of interferon-alpha on the risk of chronicity is evaluated in clinical trials. Chronic hepatitis is defined as inflammatory reaction in the liver that continues without improvement for at least 6 months after infection with hepatitis B, C or D viruses. Hepatitis B resolves in more than 90% of the patients, but chronic infection can lead to liver cirrhosis and hepatocellular carcinoma. Chronic hepatitis C is an insidious disease, because early diagnosis is missed easily due to asymptomatic presentation and about 70% of infected patients develop chronic hepatitis. The benefits of interferon-alpha and/or nucleoside analogues have been proven in recent clinical trials that show sustained responses in more than a third of all patients with chronic viral hepatitis. The future treatment of chronic viral hepatitis will likely include immunomodulation and gene therapy.

Trace elements and chronic liver diseases.

Loguercio C, De Girolamo V, Federico A, Feng SL, Cataldi V, Del Vecchio Blanco C, Gialanella G. Cattedra di Gastroenterologia, Seconda Università di Napoli, Italia.

J Trace Elem Med Biol. 1997 Nov;11(3):158-61.

The relationships between chronic liver diseases and trace element (TE) contents are debated. Particularly, no defined data are available about the TE levels in viral liver disease patients with or without malnutrition. In this study we evaluated blood and plasma levels of various trace elements in patients with HCV-related chronic liver disease, at different stages of liver damage (8 patients with chronic hepatitis and 32 with liver cirrhosis) with or without malnutrition. We also studied 10 healthy volunteers as control group. We found that cirrhotic subjects had a significant decrease of blood levels of Zn and Se, independently on the nutritional status, whereas plasma levels of Fe were significantly reduced only in malnourished cirrhotic patients. Our data indicate that liver impairment is the main cause of the blood decrease of Se and Zn levels in patients with non alcoholic liver disease, whereas the malnutrition affects Fe levels only.

Chronic hepatitis B virus infection: treatment strategies for the next millennium.

Malik AH, Lee WM. Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas 75390-9151, USA.

Ann Intern Med. 2000 May 2;132(9):723-31.

Chronic hepatitis B virus (HBV) infection is a leading cause of cirrhosis and hepatocellular carcinoma worldwide. Its prevalence

approaches 10% in hyperendemic areas, such as southeast Asia, China, and Africa. Although chronic HBV infection is seen less frequently in North America and Europe, an estimated 1.25 million persons in the United States are infected. In the past decade, revolutionary strides have been made toward the treatment of chronic HBV infection. Interferon-alpha was once the only available therapy but has recently been joined by the nucleoside analogues, the most extensively studied of which is lamivudine. Interferon therapy continues to have a role in the treatment of a carefully selected group of patients. Lamivudine therapy, which has less stringent selection criteria, suppresses HBV DNA in almost all treated patients: Seventeen percent to 33% experience loss of hepatitis B e antigen, and 53% to 56% have a histologic response. Extended lamivudine treatment leads to the development of a specific lamivudine-resistant virus with base-pair substitutions at the YMDD locus of the DNA polymerase. Newer nucleoside analogues and other immunomodulator therapies are being investigated. In the future, combination therapy with different classes of agents may yield improved response rates and delay the development of resistance.

The management of chronic hepatitis B infection.

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Int J STD AIDS. 2001 Jun;12(6):353-7.

Chronic hepatitis B infection is frequently diagnosed within the genitourinary clinic setting with sexual transmission the commonest route of acquisition in the United Kingdom. Only 3--5% of adults who contract acute hepatitis B will progress to chronic infection, and these individuals can be identified by the presence of hepatitis B surface antigen (HBsAg) in the bloodstream 6 months after infection. Individuals at highest risk of long-term complications such as cirrhosis and hepatocellular carcinoma, carry HBeAg and have high levels of circulating hepatitis B virus (HBV) deoxyribonucleic acid (DNA). Therapy should be targeted towards this group of patients. Two forms of therapy are now licensed for use in chronic hepatitis B infection: interferon-alpha and lamivudine. Seroconversion occurs in 30--40% of patients treated with interferon and treatment is often limited by toxicity. Lamivudine is well tolerated with seroconversion rates of 15--20% at one year, rising with increasing duration of therapy. Long-term monotherapy is limited however by the development of resistance mutations and combination nucleoside therapy is likely to become the treatment of choice in the future. Patients with chronic hepatitis B should be counselled regarding transmission, partner vaccination and alcohol intake and co-infection with other hepatitis viruses should be excluded.

Does hepatitis B virus (HBV) genotype influence the clinical outcome of HBV infection?

Mayerat C, Mantegani A, Frei PC. Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland.

J Viral Hepat. 1999 Jul;6(4):299-304.

Between 5 and 10% of adults infected with the hepatitis B virus (HBV) develop a chronic infection lasting longer than 6 months, which may lead to advanced liver disease. HBV can be classified into six genotypic families: A, B, C, D, E and F, but only genotypes A and D are significantly represented in western Europe, where they account for some 90% of cases of infection with HBV. In the present study, we investigated a possible association between HBV genotype A or D and clinical outcome of the infection. We compared the prevalence of these genotypes in a group of patients with chronic active hepatitis to that of a group with acute resolving hepatitis. In patients with chronic active hepatitis, genotype A was found in 28 of 35 patients and genotype D in only four. The remaining three patients were infected with genotype non-A, non-D. In contrast, genotype D was found in 24 of 30 patients with acute hepatitis, whilst genotype A was found in only three patients of this group. Three were infected with genotype non-A, non-D. Our results show a clear association between genotype A and chronic outcome (Fisher's exact test: two-sided P-value, $P < 0.0001$). They suggest that HBV genotypes may play a role in the virus-host relationship. Possible mechanisms for such a role are discussed.

Additive antiviral effects of lamivudine and alpha-interferon in chronic hepatitis B infection.

Mutimer D, Dowling D, Cane P, Ratcliffe D, Tang H, O'Donnell K, Shaw J, Elias E, Pillay D. Liver and Hepatobiliary Unit, Queen Elizabeth Hospital, Birmingham, UK. david.mutimer@university-b.wmids.nhs.uk

Antivir Ther. 2000 Dec;5(4):273-7.

alpha-Interferon has limited efficacy against chronic hepatitis B virus (HBV) infection. Nucleoside analogues may confer greater benefits, however, it is likely that combination therapies will be required for effective control of this infection. We investigated the antiviral effect of lamivudine and interferon therapy in eight patients with high HBV-DNA levels. Six patients received lamivudine/interferon combination therapy followed, after a 6-month drug-free period, with lamivudine monotherapy. Mean HBV viral load (copies/ml) reduction was significantly greater after 4 months of combination therapy ($4.3 \times 10(3)$) compared to an equivalent period of lamivudine monotherapy ($2.9 \times 10(2)$) ($P=0.03$). Two patients were given 6 months of lamivudine/interferon combination therapy followed immediately by lamivudine monotherapy. Cessation of interferon in these patients led to a rapid 1-2 log₁₀ increase

in HBV viral load. These findings suggest that alpha-interferon has a direct antiviral effect on chronic HBV infection, which may be additive to, or synergistic with lamivudine.

Reactive oxygen species and nitric oxide in viral diseases.

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Biol Trace Elem Res. 1997 Jan;56(1):107-16.

Metabolites derived from superoxide (O₂⁻) and nitric oxide (NO) play an important role in antimicrobial and antitumoral defense, but may also harm the host. Low levels of such metabolites can also facilitate viral replication because of their mitogenic effects on cells. Most viruses grow better in proliferating cells, and indeed, many viruses induce in their host cell changes similar to those seen early after treatment with mitogenic lectins. Influenza and paramyxo-viruses activate in phagocytes in the generation of superoxide by a mechanism involving the interaction between the viral surface glycoproteins and the phagocyte's plasma membrane. Interestingly, viruses that activate this host defense mechanism are toxic when injected in the bloodstream of animals. Mice infected with influenza virus undergo oxidative stress. In addition, a wide array of cytokines are formed in the lung, contributing to the systemic effects of influenza. Oxidative stress is seen also in chronic viral infections, such as AIDS and viral hepatitis. Oxidant production in viral hepatitis may contribute to the emergence of hepatocellular carcinoma, a tumor seen in patients after years of chronic inflammation of the liver. Antioxidants and agents that downregulate proinflammatory cytokines and lipid mediators may be a useful complement to specific antiviral drugs in the therapy of viral diseases.

Regulative potential of glutamine--relation to glutathione metabolism.

Roth E, Oehler R, Manhart N, Exner R, Wessner B, Strasser E, Spittler A. Department of Surgery, Research Laboratories, Vienna, Austria. e.roth@akh-wien.ac.at

Nutrition. 2002 Mar;18(3):217-21.

Glutamine (GLN) is the most abundant free amino acid (AA) in the human body. Under GLN-free conditions, which can be obtained when cells are cultivated in vitro, tissue cells cannot grow. Therefore, when classifying GLN as a "non-essential" AA, one must consider that in the human body GLN is synthesized from essential AAs and is continuously delivered from skeletal muscle to other organs. It is fascinating that a relatively simple AA like GLN can stimulate a large variety of cellular reactions. GLN stimulates not only the growth of cells but also the expression of surface antigens, the formation of cytokines, and the synthesis of heat shock proteins. Further, a GLN deficiency leads to a cell cycle arrest in G(0) to G(1) and reduces apoptosis. Interestingly, many of these biological activities also are associated with the cellular reduced oxygen potential, which depends mainly on the ratio of reduced to oxidized glutathione. Experimental animal studies have shown that the administration of GLN increases tissue concentrations of reduced glutathione. This review describes the relation of GLN to reduced glutathione metabolism and discusses the alteration of reduced glutathione metabolism under a variety of clinical conditions such as reperfusion injury, myocardial infarction, respiratory insufficiency, cancer, diabetes, liver disease, and clinical protein catabolism.

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.

No Abstract available.

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

Valenzuela A, Garrido A. Unidad de Bioquímica Farmacológica y Lípidos, Universidad de Chile, Santiago.

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

The flavonoid silymarin and one of 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.

Vitamin E improves the aminotransferase status of patients suffering from viral hepatitis C: a randomized, double-blind, placebo-controlled study.

von Herbay A, Stahl W, Niederau C, Sies H. Department of Internal Medicine (GI-Unit), Heinrich-Heine-Universität Düsseldorf, Germany.

Free Radic Res. 1997 Dec;27(6):599-605.

Vitamin E has been shown to protect against liver damage induced by oxidative stress in animal experiments. Based on our previous findings of diminished vitamin E levels in patients suffering from viral hepatitis, we treated 23 hepatitis C patients refractory to alpha-interferon therapy with high doses of vitamin E (2 x 400 IU RRR-alpha-tocopherol/day) for 12 weeks. Study design: prospective randomized double-blind crossover design. Clinical parameters including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined for monitoring the disease state, in parallel vitamin E plasma levels and plasma lipids were determined. The plasma levels of the alpha-tocopherol were increased about 2-fold in all 23 patients. In 11 of 23 patients the clinical parameters indicative of liver damage were improved during the phase of vitamin E treatment (48% responders). ALT levels in responders were lowered by 46% and AST levels were lowered by 35% after 12 weeks of vitamin E treatment. Cessation of vitamin E treatment was followed by a rapid relapse of ALT and AST elevation, whereas retreatment led to a reproducible ALT decrease by 45% and AST decrease of 37% after a 6 months followup. Since vitamin E is non-toxic even at elevated doses ingested over extended periods, we suggest the treatment of patients refractory to alpha-interferon therapy suffering from hepatitis C with vitamin E as a supportive therapy.

[Alanyl-glutamine dipeptides protected the liver function by increasing the hepatic glutathione] [Article in Chinese]

Yu J, Jiang Z, Li D, Yang N, Bai M. PUMC Hospital, CAMS and PUMC, Beijing 100730.

Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 1998 Apr;20(2):103-8.

OBJECTIVE: Glutathione (GSH) is a major antioxidant which protects hepatic tissues from free radical injury. Alanyl-Glutamine (ALA-GLN) proved to be a precursor of GSH synthesis, was used to investigate the relationship to GSH biosynthesis which may be effective for hepatic protection. **METHODS:** 20 male Wistar rats were randomly divided into two groups receiving standard parenteral nutrition (STD) supplemented with or without ALA-GLN for 7 days. At 5th day 5-fluorouracil (5-FU) was injected peritoneally, the blood samples for GSH, GSSG, ALT (sGPT), AKP and TBilli tests were measured after 4-8 h. **RESULTS:** The concentration measurements were significantly different in ALA-GLN group compared with STD animals in serum GLN (687.3 +/- 49.8) vs (504.9 +/- 38.6) $\mu\text{mol/L}$, $P < 0.05$, serum GSH (14.37 +/- 5.16) vs (7.08 +/- 3.16) $\mu\text{mol/L}$, $P < 0.01$) and in liver GSH content (6.86 +/- 2.46) vs (4.38 +/- 1.63) $\mu\text{mol/g}$ liver tissue, $P < 0.05$). Rats in ALA-GLN group have lesser elevations in hepatic enzymes after 5-FU administration. **CONCLUSIONS:** The supplemented nutrition ALA-GLN protected the liver function through increasing the glutathione biosynthesis and preserving the glutathione stores of hepatic tissue.

Glutamine: a precursor of glutathione and its effect on liver.

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World J Gastroenterol. 1999 Apr;5(2):143-146.

AIM:To investigate the relationship between alanyl-glutamine (ALA-GLN) and glutathione (GSH) biosynthesis in hepatic protection. **METHODS:** Twenty male Wistar rats were randomly divided into two groups: one receiving standard parenteral nutrition (STD) and the other supplemented with or without ALA-GLN for 7 days. The blood and liver tissue samples were examined after 5-fluorouracil (5-FU) was injected peritoneally. **RESULTS:** The concentration measurements were significantly higher in ALA-GLN group than in STD group in serum GLN (687 < $\mu\text{mol/L}$ plus minus 50 < $\mu\text{mol/L}$ vs 505 < $\mu\text{mol/L}$ plus minus 39 < $\mu\text{mol/L}$, $P < 0.05$), serum GSH (14 < $\mu\text{mol/L}$ plus minus 5 < $\mu\text{mol/L}$ vs 7 < $\mu\text{mol/L}$ plus minus 3 < $\mu\text{mol/L}$, $P < 0.01$) and in liver GSH content (6.9 < $\mu\text{mol/g}$ plus minus 2.5 < $\mu\text{mol/g}$ vs 4.4 < $\mu\text{mol/g}$ plus minus 1.6 < $\mu\text{mol/g}$ liver tissue, $P < 0.05$). Rats in ALA-GLN group had lesser elevations in hepatic enzymes after 5-FU administration. **CONCLUSION:** The supplemented nutrition ALA-GLN can protect the liver function through increasing the glutathione biosynthesis and preserving the glutathione stores in hepatic tissue.

Chemoprevention trial of human hepatitis with selenium supplementation in China.

Yu SY, Li WG, Zhu YJ, Yu WP, Hou C Cancer Institute Chinese Academy of Medical Sciences, Beijing.

Biol Trace Elem Res 1989 Apr-May;20(1-2):15-22

A three-year study has been conducted for prevention of infectious hepatitis with supplementation of table salt fortified with 15 ppm anhydrous sodium selenite to the general population of 20,847 persons in a township M.Z. at Qidong County, Jiangsu Province, China. The results showed that the incidence of virus hepatitis infection in the test township was significantly lower than that of controls provided with normal table salt. The incidence rate of infectious hepatitis in the treated township M.Z. was 1.20 and 4.52 per 1,000, whereas the average incidence in the 6 surrounding control townships was 2.96 and 10.48 per 1,000 in 1986 and 1987, respectively. The incidence of hepatitis B surface antigen (HBsAg+) was 13.2% vs 19.23% for males and 10.42% vs 12.24% for females in the supplemented vs nonsupplemented neighboring township, respectively. Epidemiological studies have demonstrated that a low grain Se content is associated with a high regional incidence of hepatitis B virus infections.

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

Yu SY, Zhu YJ, Li WG Cancer Institute, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China.

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.

SUGGESTED READING

Hepatic glutathione content in patients with alcoholic and non alcoholic liver diseases.

Altomare E, Vendemiale G, Albano O. Istituto di Clinica Medica I, Universita' di Bari, Italy.

Life Sci 1988;43(12):991-8

Reduced and oxidized hepatic glutathione was evaluated during alcoholic and non alcoholic liver injury. We studied 35 chronic alcoholics, 20 patients with non alcoholic liver diseases, 15 control subjects. Hepatic glutathione was measured in liver biopsies and correlated with histology and laboratory tests. Alcoholic and non alcoholic patients exhibited a significant decrease of hepatic glutathione compared to control subjects (controls: 4.14 0.1 $\mu\text{mol/g}$ liver; alcoholics: 2.55 0.1, p less than 0.001; non alcoholics 2.77 0.1, p less than 0.001). Oxidized glutathione was significantly higher in the two groups of patients compared to controls (controls: 4.4 0.2% of total; alcoholics 8.2 0.3, p less than 0.001; non alcoholics: 8.5 0.8, p less than 0.001). The decreased hepatic glutathione levels in patients with alcoholic and non alcoholic liver diseases may represent a contributing factor of liver injury and may enhance the risk of toxicity in these patients.

Thymosin alpha in the treatment of chronic hepatitis B: an uncontrolled open-label trial.

Amarapurkar D, Das HS. Bombay Hospital and Research Center, Mumbai.

Indian J Gastroenterol 2002 Mar-Apr;21(2):59-61

BACKGROUND: Interferon treatment for chronic hepatitis B has low efficacy and is associated with serious side effects. It is therefore important to assess the role of other drugs in the treatment of this condition. **AIMS:** To assess the efficacy and safety of thymosin alpha in 20 patients with hepatitis B-related liver disease. **METHODS:** Patients with chronic hepatitis B, HBV DNA positivity, ALT more than 1.5 times the upper limit of normal and liver biopsy showing chronic hepatitis or cirrhosis were treated with thymosin alpha 1.6 mg subcutaneously twice a week for 6 months. Biochemical and serological markers were assessed pre-treatment, immediately post treatment, and 6 months and 1 year after end of treatment. **RESULTS:** Of 20 patients, 15 had chronic

hepatitis and 5 had cirrhosis on histology; 17 were HBeAg-positive and 3 were HBeAg-negative. Eight patients were interferon non-responders and 12 were naive patients. Four patients had end-of-treatment response and two additional patients had a delayed response within 6 months of treatment; one responder had a relapse within 1 year of treatment. Overall sustained response rate was 25% (5 of 20). No patient cleared HBsAg. Reduction in ALT levels was observed after treatment and persisted one year later. No significant side effects were observed. CONCLUSION: Thymosin alpha is a safe and effective alternative treatment modality in chronic hepatitis B.

Centrilobular endothelial cell injury by diquat in the selenium-deficient rat liver.

Atkinson JB, Hill KE, Burk RF. Department of Pathology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.

Lab Invest 2001 Feb;81(3):193-200

Low doses of diquat cause massive liver necrosis and death of selenium-deficient rats within a few hours. Protection against this injury by selenium correlates with the presence of selenoprotein P, an extracellular selenoprotein that associates with endothelial cells. Selenium-deficient rats were injected with diquat (10 mg/kg) and their livers were removed for light and electron microscopy at times up to 120 minutes after injection. Selenium-replete animals were studied before and 120 minutes after the same dose of diquat. With selenium deficiency, diquat caused injury to centrilobular endothelial cells. This injury was evident 20 minutes after diquat injection and progressed to cell loss at 60 minutes after diquat injection. At 120 minutes, endothelial cells were virtually absent from the centrilobular regions and hepatocytes in those areas were undergoing necrosis. Portal and midzonal areas remained normal in selenium-deficient livers, as did the entire liver lobule of selenium-replete rats. These findings indicate that the initial liver lesion in selenium-deficient rats given diquat is injury of the endothelial cells in the centrilobular region. After detachment of the endothelial cells, centrilobular hepatocytes undergo necrosis. We postulate that selenoprotein P protects the centrilobular endothelial cells against injury by oxidant molecules that result from diquat administration.

[Clinical study of 96 cases with chronic hepatitis B treated with jiedu yanggan gao by a double-blind method]. [Article in Chinese]

Chen Z Dept. of Hepatic Diseases, Beijing TCM Hospital.

Zhong Xi Yi Jie He Za Zhi 1990 Feb;10(2):71-4, 67

This paper reported 96 cases with chronic hepatitis B treated by a double-blind method. There were 51 cases of observation group (OG) and 45 cases of control group (CG). OG was treated with Jiedu Yanggan Gao consisting of *Artemisia capillaris*, *Taraxacum mongolicum*, *Plantago seed*, *Cephalanoplos segetum*, *Hedyotis diffusa*, *Flos Chrysanthemi Indici*, *Smilax glabra*, *Astragalus membranaceus*, *Salviae miltiorrhizae*, *Fructus Polygonii Orientalis*, *Radix Paeoniae Alba*, *Polygonatum sibiricum*, etc.). CG was prescribed with three charred medicinal herbs (charred *Fructus Crataegi*, charred *Fructus Hordei Germinatus*, charred fermented mixture of several medical herbs and wheat bran). The average duration of treatment was five months. All 96 cases belong to the virus-duplication-type with positive HBsAg for over one year. Among them 65.5% of cases HBeAg, DNAP and HBV-DNA were positive. 20.8% of cases were positive in two out of the above tests. 13 data were compared statistically between two groups, and proved to be comparable (P greater than 0.05) before treatment. 27.3% and 66.7% of cases' ALT, AST returned to normal respectively in OG after treatment. However, in CG they were 9.1% and 22.2% (P less than 0.05). TTT returned to normal in 52% cases of OG and 44% in CG (P greater than 0.05). 20% cases HBeAg shifted to negative in OG, but 6.7% in CG. Cases with negative DNAP in OG occupied 34.2%, but 10.8% in CG. 31.6% cases' HBV-DNA changed to negative in OG, while 17.6% in CG. After comprehensive judgement, the total effective rate was 74.5% in OG and 24.4% in CG respectively (P less than 0.001). Eight cases were basically cured in OG and one case in CG. After one year's follow-up, one recurred in eight patients of OG, however the only one cured in CG still relapsed.

Efficacy of thymosin alpha1 in patients with chronic hepatitis B: a randomized, controlled trial.

Chien RN, Liaw YF, Chen TC, Yeh CT, Sheen IS. Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University, Taipei, Taiwan.

Hepatology 1998 May;27(5):1383-7

Thymosin alpha1 (Talpa) is an immune modifier that has been shown in a pilot study to be effective for chronic hepatitis B; this requires confirmation. Ninety-eight patients with clinicopathologically proven chronic hepatitis B were randomly allocated to 3 groups: 1) group A received a 26-week course of Talpa with a 1.6-mg subcutaneous injection two times a week (T6 group); 2) group B received the same regimen as group A, but Talpa therapy extended for 52 weeks (T12 group); and 3) group C served as a control group and was followed up for 18 months without specific treatment (T0 group). The three groups were comparable in clinicohistological features at entry. The complete virological response rate (clearance of serum hepatitis B virus [HBV] DNA and hepatitis B e antigen [HBeAg]) was higher in group A (40.6%) and group B (26.5%) than in group C (9.4%) (group A vs. group C:

P=.004; group B vs. group C: P=.068) when assessed 18 months after entry, although complete response rates among these three groups were similar when first assessed at the end of therapy. There was a trend for complete virological response to increase or accumulate gradually after the end of Talpha therapy. None of the responders lost hepatitis B surface antigen. Blinded histological assessment showed a significant improvement in treated patients, particularly in lobular necroinflammation and scores excluding fibrosis. No significant side effects were observed. These results suggest that a 26-week course of Talpha therapy is effective and safe in patients with chronic hepatitis B.

Bioactivity of neolignans from fructus Schizandrae.

Li XY Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

Mem Inst Oswaldo Cruz 1991;86 Suppl 2:31-7

Fructus Schizandrae sinensis Baill, a traditional Chinese medicine, used as tonic and sedative, has been shown at the beginning of 70's to lower the elevated serum glutamic-pyruvic transaminase (SGPT) levels of patients suffering from chronic viral hepatitis. During past 20 years, a series of neolignans have been isolated and identified as effective principles. Pharmacological studies revealed that they increased liver protein and glycogen synthesis, antagonized liver injuries from CCl₄ and thioacetamide. The mechanism of SGPT lowering was considered as a hepato-protective and membrane stabilize action, although inhibition of the activity of liver GPT may also be existed. It was found that some principles of Schizandrae have an inducing effect on hepatic microsomal drug-metabolizing enzyme system P-450, thus explained their anti-toxic, anti-carcinogenic and anti-mutagenic effects. A synthetic derivative compound of Schisandrin called DDB has most of the above mentioned actions now used widely in China as a hepato-protective drug with high effectiveness in normalizing liver functions and very low side effects. From natural Schisandrin to synthesized DDB, pointed out a successful way in the development of new drugs from natural products.

Pharmacological properties of Dibenzo[a,c]cyclooctene derivatives isolated from Fructus Schizandrae Chinensis III. Inhibitory effects on carbon tetrachloride-induced lipid peroxidation, metabolism and covalent binding of carbon tetrachloride to lipids.

Liu KT, Lesca P

Chem Biol Interact 1982 Jul 15;41(1):39-47

Fructus Schizandrae, a traditional Chinese tonic, has been shown to lower the elevated serum glutamic pyruvic transaminase (SGPT) levels of patients with chronic viral hepatitis and several of its components decrease the hepatotoxicity of carbon tetrachloride (CCl₄) in animals. This paper deals with the mechanism of protection against CCl₄-hepatotoxicity of these compounds as well as of DDB, a synthetic analogue of Schisandrin (Sin) C. Of the seven components, Sin B and C, Schizandrol (Sol) B, Schizandrer (Ser) A and B, as well as dimethyl-4,4'-dimethoxy-5,6,5',6'-dimethylenedioxy-biphenyl-2,2'-dicarboxylate (DDB) were shown to inhibit CCl₄-induced lipid peroxidation and [¹⁴C]CCl₄ covalent binding to lipids of liver microsomes from phenobarbital(PB)-treated mice. The compounds also decreased carbon monoxide (CO) production and cofactor (NADPH, oxygen) utilization during CCl₄ metabolism by liver microsomes. It may be postulated, therefore, that the hepatoprotective effect of certain components isolated from Fructus Schizandrae as well as DDB is due to their inhibitory effect on CCl₄-induced lipid peroxidation and the binding of CCl₄-metabolites to lipids of liver microsomes.

Glutamine and its relationship with intracellular redox status, oxidative stress and cell proliferation/death.

Mates JM, Perez-Gomez C, Nunez de Castro I, Asenjo M, Marquez J. Department of Molecular Biology and Biochemistry, Faculty of Sciences, University of Malaga, Campus de Teatinos, s/n 29071 Malaga, Spain. jmates@uma.es

Int J Biochem Cell Biol 2002 May;34(5):439-58

Glutamine is a multifaceted amino acid used for hepatic urea synthesis, renal ammoniogenesis, gluconeogenesis in both liver and kidney, and as a major respiratory fuel for many cells. Decreased glutamine concentrations are found during catabolic stress and are related to susceptibility to infections. Besides, glutamine is not only an important energy source in mitochondria, but is also a precursor of the brain neurotransmitter glutamate, which is likewise used for biosynthesis of the cellular antioxidant glutathione. Reactive oxygen species, such as superoxide anions and hydrogen peroxide, function as intracellular second messengers activating, among others, apoptosis, whereas glutamine is an apoptosis suppressor. In fact, it could contribute to block apoptosis induced by exogenous agents or by intracellular stimuli. In conclusion, this article shows evidences for the important role of glutamine in the regulation of the cellular redox balance, including brain oxidative metabolism, apoptosis and tumour cell proliferation.

Roles of selenium in endotoxin-induced lipid peroxidation in the rats liver and in nitric oxide production in J774A.1

cells.

Sakaguchi S, Iizuka Y, Furusawa S, Tanaka Y, Takayanagi M, Takayanagi Y. First Department of Hygienic Chemistry, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan.

Toxicol Lett 2000 Dec 20;118(1-2):69-77

We examined the role of selenium (Se) in the mechanism of oxidative stress caused by endotoxin by feeding rats deficient a diet in this element. In rats fed the Se-deficient diet (concentration of Se, less than 0.027 microg g(-1)) for 10 weeks, Se level and glutathione peroxidase (GSH-Px) activity in the liver were about 47 and 43% lower, respectively, than those in rats fed a Se-adequate diet (Se, 0.2 microg g(-1)). Rat fed the Se-deficient diet and given endotoxin (6 mg kg(-1), i.p.) showed a mortality rates of about 43% at 18 h. Nevertheless, no lethality was observed with endotoxin (4 mg kg(-1), i.p.) challenge. Levels of serum lactate dehydrogenase and acid phosphatase leakage were significantly higher in Se-deficient rats than those in Se-adequate diet 18 h after endotoxin (4 mg kg(-1), i. p.) challenge. Superoxide anion generation and lipid peroxide formation in the liver of Se-deficient rat were markedly increased 18 h after endotoxin (4 mg kg(-1), i.p.) injection compared with those in the endotoxin/Se-adequate diet group, whereas non-protein sulfhydryl level in the liver after administration of endotoxin to Se-deficient rats was lower than that in Se-adequate rats treated with endotoxin. We investigated whether Se can suppress nitric oxide (NO) generation and cytotoxicity in endotoxin-treated J774A.1 cells. Treatment with Se (10(-6) M) markedly inhibited endotoxin (0.1 microg ml(-1))-induced NO production in J774A.1 cells. Se induced an increased activity of GSH-Px in cells after 24 h of incubation, suggesting that the preventive effect of Se on NO production in endotoxemia is due to the induction of Se-GSH-Px activity. However, Se did not affect endotoxin-induced cytotoxicity in J774A.1 cells. These findings suggested that the oxidative stress caused by endotoxin may be due, at least in part, to changes in Se regulation during endotoxemia.

Effects of kampo (Japanese herbal) medicine "sho-saiko-to" on DNA-synthesizing enzyme activity in 1,2-dimethylhydrazine-induced colonic carcinomas in rats.

Sakamoto S, Mori T, Sawaki K, Kawachi Y, Kuwa K, Kudo H, Suzuki S, Sugiura Y, Kasahara N, Nagasawa H Medical Research Institute, Tokyo Medical and Dental University, Japan.

Planta Med 1993 Apr;59(2):152-4

Sho-Saiko-To (SST) is a modified Japanese traditional Chinese herbal medicine containing seven medical plants: Bupleuri radix, Pinelliae tuber, Suxtallariae radix, Zizyphi fructus, Ginseng radix, Glycyrrhizae radix, and Zingiberis recens rhizoma. This preparation has been used in the treatment of some inflammatory diseases of the respiratory system and chronic hepatitis. In the present study, the effects of SST were investigated on the activities of DNA-synthesizing enzymes in 1,2-dimethylhydrazine (DMH)-induced colonic carcinomas in rats. Six-week administration of SST prevented nearly 100% of the body weight loss and the final number of the colonic carcinomas compared to those in the rats treated with DMH alone, and suppressed the enhanced activities of thymidylate synthetase (TS) and thymidine kinase (TK) which were involved in the de novo and salvage pathways of pyrimidine synthesis, respectively, in DMH-induced colonic carcinomas. These results indicate that SST may show directly and/or indirectly inhibitory effects on the development of colonic carcinomas.

Compromised hepatic detoxification in companion animals and its correction via nutritional supplementation and modified fasting.

Scanlan N. American Holistic Veterinary Medical Association, USA.

Altern Med Rev 2001 Sep;6 Suppl:S24-37

Dietary components play a crucial role in the health of companion animals, especially those exposed to elevated levels of toxins and free radicals. Investigation into animals' hepatic antioxidant and metabolite conjugation systems, and the metabolic processes that influence them, provides some understanding regarding the relationship of diet to disease prevention and treatment. A review of current literature and research publications suggests nutritional supplementation can be an effective treatment for animals suffering from increased oxidative stress and toxicity. The results of recent in vivo assessments, clinical trials, and observational studies show oral supplementation with vitamin E, selenium, glutathione, and taurine to be beneficial for both maintaining natural antioxidant systems and protecting against a number of degenerative diseases associated with free radical damage and toxin exposure. In many instances, it has been observed that the introduction of specific nutrients positively influences the health status, symptomatic presentation, and life span of animals whose natural detoxification systems are compromised.

Reduced glutathione concentration in erythrocytes of patients with acute and chronic viral hepatitis.

Swietek K, Juszczak J. Department of Infectious Diseases, Karol Marcinkowski University of Medical Sciences, Poznan, Poland.

Reduced glutathione (GSH), the main intracellular mechanism that protects against oxidative stress, is the subject of considerable interest in viral hepatitis. In patients with chronic hepatitis C, results reported from different centres are controversial, demonstrating either a reduction or an elevation of GSH concentration. The aim of this study was to evaluate the glutathione concentration in erythrocytes (normal range 2.45-0.15 mmol l⁻¹) in patients with acute and chronic viral hepatitis. In 52 patients with acute viral hepatitis (hepatitis A virus (HAV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection) there was marked reduction of GSH at the beginning of the disease (0.79-0.43 mmol l⁻¹, $P < 0.001$) with high alanine aminotransferase (ALT) activity (1549-772.9 IU l⁻¹). In 37 patients with chronic HCV infection the mean value of GSH was below the normal range (1.92-0.62 mmol l⁻¹, $P < 0.001$). In 60% of patients ($n = 22$), depletion of GSH was observed and 40% ($n = 15$) presented with a normal concentration of GSH. In 10 patients with chronic HBV infection the mean value of GSH was also below the normal range (1.93-0.32 mmol l⁻¹, $P < 0.001$); in 80% of cases ($n = 8$) depletion of GSH was observed and 20% of patients ($n = 2$) had normal GSH concentrations. The ALT activity was not significantly different in patients with depleted and normal GSH concentrations ($P > 0.05$) in groups with chronic HBV and HCV infection.

The effects of chronic hepatitis C and B virus infections on liver reduced and oxidized glutathione concentrations.

Tanyalcin T, Taskiran D, Topalak O, Batur Y, Kutay F. Department of Biochemistry, Ege University School of Medicine, Bornova 35100, Izmir, Turkey

Hepatol Res 2000 Aug;18(2):104-109

The aim of this study was to evaluate the effects of hepatitis B and C virus infections on liver glutathione status. Reduced and oxidized glutathione levels were determined in liver biopsy specimens obtained from patients with chronic liver disease including chronic active hepatitis and cirrhosis. In patients with hepatitis B virus infections, GSH and GSH/GSSG levels were significantly low compared with those in controls ($P < 0.01$). There was a significant negative correlation between histological activity indices (HAI) and hepatic GSSG levels only in patients with chronic HCV infection ($P < 0.01$; $r = -0.895$). In addition to this, we also found a positive correlation between indices (HAI) and GSH/GSSG of the same group ($r = 0.915$; $P < 0.05$). These observations suggest that HBV and HCV infections have different effects on liver glutathione status based on diverse mechanisms.

Evidence of hepatic endogenous hydrogen peroxide in bile of selenium-deficient rats.

Ueda Y, Matsumoto K, Endo K. Department of Physical Chemistry, Showa Pharmaceutical University, 3-3165, Higashi-Tamagawagakuen, Machida, Tokyo, 194-8543, Japan.

Biochem Biophys Res Commun 2000 May 19;271(3):699-702

Hepatic endogenous hydrogen peroxide (H₂O₂) in bile of selenium-deficient rats (SeD) was for the first time found using the electron spin resonance (ESR) spin-trap technique, and the relationship between glutathione peroxidase (GPX) activity and H₂O₂ amount is discussed. Normal rats and four groups of rats fed a selenium-deficient diet with different feeding periods were examined. The results showed that the GPX activity decreased depending on the feeding period with the selenium-deficient diet and that the hepatic endogenous H₂O₂ amount in the bile of the rats fed the selenium-deficient diet for the longest period (a week before birth to 8 weeks old) was drastically higher than those in other groups of rats ($P < 0.005$). We found that generation of H₂O₂ due to the decrease in the GPX activity has a threshold value. The results suggest that an exposure to selenium deficiency for long term will cause oxidative stress. Copyright 2000 Academic Press.

Glutathione S-transferase expression in hepatitis B virus-associated human hepatocellular carcinogenesis.

Zhou T, Evans AA, London WT, Xia X, Zou H, Shen F, Clapper ML. Division of Population Science, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111, USA.

Cancer Res 1997 Jul 1;57(13):2749-53

Hepatitis B virus (HBV) and aflatoxin B₁ represent the main risk factors for the development of hepatocellular carcinoma (HCC) in areas endemic for liver cancer. The glutathione S-transferases (GSTs) are a family of Phase II detoxification enzymes that catalyze the conjugation of a wide variety of endogenous and exogenous toxins, including aflatoxin B₁, with glutathione. This study characterizes the GST isoenzyme composition (alpha, mu, and pi) of both HBV-infected normal hepatic tissues and HCCs. Analysis of matched pairs of hepatic tissue (normal and tumor) from 32 HCC patients indicated that total GST activity was significantly higher in normal tissues than in tumor tissues, although the percentage of samples expressing GST alpha and pi was equivalent. GST mu was detected by Western blot in the normal tissue from 87.5% of the subjects possessing the GST M1 gene but only 28.6% of the corresponding tumor tissues. The GST activity of normal tissue from GST M1 null patients was significantly

decreased as compared to that of subjects possessing the GST M1 gene (264.6 and 422.2 nmol/min/mg, respectively; $P = 0.005$). GST pi appeared to be overexpressed in the normal tissue of GST M1 null patients, a potential compensatory effect. Patients positive for HBV DNA had significantly lower GST activity than those who were HBV negative (302.1 versus 450.0 nmol/min/mg, respectively; $P = 0.02$). These results suggest that cellular protection within the human liver is compromised by HBV infection and further decreased during hepatocellular tumorigenesis.

HEPATITIS B (Page 2)

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Iron in liver diseases other than hemochromatosis

Bonkovsky HL, Banner BF, Lambrecht RW, Rubin RB
 Department of Medicine, University of Massachusetts Medical Center, Worcester 01655, USA.
 Semin Liver Dis 1996 Feb;16(1):65-82

There is growing evidence that normal or only mildly increased amounts of iron in the liver can be damaging, particularly when they are combined with other hepatotoxic factors such as alcohol, porphyrogenic drugs, or chronic viral hepatitis. Iron enhances the pathogenicity of microorganisms, adversely affects the function of macrophages and lymphocytes, and enhances fibrogenic pathways, all of which may increase hepatic injury due to iron itself or to iron and other factors. Iron may also be a co-carcinogen or promoter of hepatocellular carcinoma, even in patients without HC or cirrhosis. Based on this and other evidence, we hope that the era of indiscriminate iron supplementation will come to an end. Bloodletting, a therapy much in vogue 2 centuries ago, is deservedly enjoying a renaissance, based on our current understanding of the toxic effects of iron and the benefits of its depletion.

[Markers of chronic hepatitis B in children after completion of therapy with isoprinosine]

Kowalik-MikoLajewska B; Barszcz T; Ladyzynska E; Wojnarowski M
 Kliniki C Chorob Zakaznych i Paso.ANG.zytnicznych Wieku Dzieciecego Instytutu Chorob Zakaznych i Paso.ANG.zytnicznych AM, Warszawa.
 Pol Tyg Lek (Poland) Mar 15-29 1993, 48 (11-13) p263-4

Fourteen children with chronic active hepatitis B treated with isoprinosine were followed-up for 3-8 years. In no child HBs antigen was eliminated. No seroconversion was noted in children in whom HBe antigen was eliminated. Anti-HBe antibodies were found in 11 children, including 6 children in whom they were present all the time following therapy, and 2 children in whom these antibodies reappeared after an initial elimination. These results suggest that the inhibition of hepatitis B virus replication produced by isoprinosine may be transient. Therefore, longer lasting immunomodulating therapy should be considered.

[Course of chronic virus hepatitis B in children and attempts at modifying its treatment]

Kowalik-Mikołajewska B
Kliniki Chorob Zakaznych i Paso. ANG. z ytnicznych Wieków Dzieci
Pol Tyg Lek (Poland) Mar 15-29 1993, 48 (11-13) p258-60

60 children with chronic virus hepatitis B were followed from there to nine years. 34 children received isoprinosine, 6 prednisone and 20 children were without any therapy. There were no cases of death. In 2 cases treated with isoprinosine cirrhosis was found. Eight children with chronic active hepatitis (4 treated with isoprinosine, 1 with prednisone, and 3 without any treatment) had histological recovery. Isoprinosine significantly accelerated seroconversion in HBe system in children with chronic active hepatitis but not in children with persistent, hepatitis. Isoprinosine shortened also the time of normalisation of aminotransferases activity children. Prednisone had no influence on the course of chronic active hepatitis B in treated group.

Isoprinosine in the treatment of chronic active hepatitis type B.

Cianciara J; Laskus T; Gabinska E; Loch T
Scand J Infect Dis (Sweden) 1990, 22 (6) p645-8

21 patients with chronic active hepatitis B (CAH-B) were treated for 1-2 years with isoprinosine, while another 18 patients served as control group. All patients were initially DNA polymerase (DNAP) and HBeAg positive. Nine (43%) treated patients became persistently negative for DNAP, seroconverted to anti-HBe and showed histological remission on follow-up biopsy. Among simultaneously followed controls 5 (28%) lost DNAP and 4 (22%) also lost their HBeAg. However, only 2 (11%) seroconverted to anti-HBe. Histological improvement was seen in 5 (28%) controls. Thus, it seems that isoprinosine may exert a beneficial effect on the course and outcome of CAH-B.

[Evaluation of the treatment of chronic active hepatitis (HBsAg+) with isoprinosine. II. Immunological studies]

Dabrowska-Bernstein B; Stasiak A; Dabrowski M; Pawinska A; Cianciara J; Loch T; Babiuch L
Pol Tyg Lek (Poland) Apr 16-30 1990, 45 (16-18) p347-51

A two-month treatment of the chronic active hepatitis (HBsAg+) with isoprinosine produced quantitative and functional T-cells populations in patients with cellular response disorders. Immunological studies have shown that such an effect of isoprinosine lasted for about 4-5 months. Repeated administration of isoprinosine for one month normalized recurrent abnormalities in the monitored immunological parameters.

In vitro studies on the effect of certain natural products against hepatitis B virus.

Mehrotra R; Rawat S; Kulshreshtha DK; Patnaik GK; Dhawan BN
Indian J Med Res (India) Apr 1990, 92 p133-8

Picroliv (active principle from *Picrorrhiza kurroa*), its major components picroside I, catalpol, kutkoside I, kutkoside, andrographolide (active constituent of *Andrographis paniculata*), silymarin and *Phyllanthus niruri* extract were tested for the presence of anti hepatitis B virus surface antigen (anti HBs) like activity. HBsAg positive serum samples obtained from hepatitis B virus (HBV) associated acute and chronic liver diseases and healthy HBsAg carriers were used to evaluate the anti-HBs like activity of compounds/extract. The latter were mixed with serum samples and incubated at 37 degrees C overnight followed by HBsAg screening in the Elisa system. A promising anti-HBsAg like activity was noted in picroliv (and its major components) catalpol, P. niruri which differed from the classical viral neutralization. Picroliv also inhibited purified HBV antigens (HBsAg and HBcAg) prepared from healthy HBsAg carriers. The in vitro testing system appears to be a suitable model to identify an agent

active against HBV, prior to undertaking detailed studies.

Effects of glycyrrhizin on hepatitis B surface antigen: a biochemical and morphological study.

Takahara T; Watanabe A; Shiraki K
J Hepatol (Denmark) Oct 1994, 21 (4) p601-9

Glycyrrhizin, a major component of a herb (licorice), has been widely used to treat chronic hepatitis B in Japan. This substance improves liver function with occasional complete recovery from hepatitis; its effects on the secretion of hepatitis B surface antigen (HBsAg) were examined *in vitro*. Glycyrrhizin suppressed the secretion of HBsAg and accumulated it dose-dependently in PLC/PRF/5 cells. Its action was further analyzed and determined in the HBsAg-expression system using the varicella-zoster virus. Glycyrrhizin suppressed the secretion of HBsAg, resulting in its accumulation in the cytoplasmic vacuoles in the Golgi apparatus area. HBsAg labeled with ³⁵S-methionine and cysteine accumulated in the cells and its secretion was suppressed dose-dependently in glycyrrhizin-treated culture. The secreted HBsAg was modified by N-linked and O-linked glycans but its sialylation was inhibited dose-dependently by glycyrrhizin. Thus glycyrrhizin suppressed the intracellular transport of HBsAg at the trans-Golgi area after O-linked glycosylation and before its sialylation. HBsAg particles were mainly observed on the cell surface in the glycyrrhizin-treated culture but not in the untreated culture. This suggests that asialylation of HBsAg particles resulted in the novel surface nature of glycyrrhizin-treated HBsAg particles. We elucidated the unique mechanism of action of glycyrrhizin on HBsAg processing, intracellular transport, and secretion.

Glycyrrhizin withdrawal followed by human lymphoblastoid interferon in the treatment of chronic hepatitis B.

Hayashi J; Kajiyama W; Noguchi A; Nakashima K; Hirata M; Hayashi S; Kashiwagi S
Gastroenterol Jpn (Japan) Dec 1991, 26 (6) p742-6

Seventeen patients with chronic hepatitis B were treated with a 4-week administration of glycyrrhizin followed by a 4-week treatment with human lymphoblastoid interferon, then followed for 6 months after the end of treatment. All were positive for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and hepatitis B virus-associated DNA polymerase (DNA-p) for at least 6 months before entry. All patients were Japanese and none of them were homosexuals. Eleven patients lost DNA-p activity and 10 of them lost HBeAg. Three of these 10 patients had antibody to HBeAg. In 10 patients who became HBeAg-negative, alanine aminotransferase levels after glycyrrhizin administration were higher and initial DNA-p activities relatively lower than the levels found in seven patients who remained HBeAg-positive. The immunomodulator provided by a short course of glycyrrhizin before administration of human lymphoblastoid interferon may be an effective treatment for patients with chronic hepatitis B.

Combination therapy of glycyrrhizin withdrawal and human fibroblast Interferon for chronic hepatitis B.

Hayashi J; Kashiwagi S; Noguchi A; Ikematsu H; Tsuda H; Tsuji Y; Motomura
Clin Ther (United States) 1989, 11 (1) p161-9

In ten carriers positive for chronic hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and DNA polymerase, the authors investigated the efficacy of the combination therapy consisting of glycyrrhizin withdrawal and human fibroblast interferon (locally produced). Glycyrrhizin was given for four weeks and was stopped without tapering off the dose. Human fibroblast interferon was given continuously. Thirty-six weeks after the end of this treatment, three of the ten patients were HBeAg negative but not anti-HBe positive, and in one of these three DNA polymerase became undetectable. Another patient showed a loss of DNA polymerase with HBeAg. Transaminase levels decreased in nine of the patients. Glycyrrhizin appeared to act as an antiviral agent in four patients and had a corticoid-like effect in three. DNA polymerase decreased remarkably after interferon administration, and serum transaminase levels increased. No side effects were reported in patients receiving glycyrrhizin. In contrast, almost all patients receiving human fibroblast interferon had influenza-like symptoms, which, although initially severe, decreased with subsequent injections of interferon. Thus this combination therapy seems safe and effective.

Alpha-interferon combined with immunomodulation in the treatment of chronic hepatitis B.

Peters M
J Gastroenterol Hepatol (Australia) 1991, 6 Suppl 1 p13-4

Interferon has profound anti-viral, anti-proliferative and immunomodulatory effects. Future studies should be directed at observing how the immunomodulatory effects predict a response in certain groups of patients. Interferon is very useful in chronic hepatitis B but may require the addition of a steroid pulse. Individuals with low serum ALT appear to benefit most from a steroid pulse. Therapy should be given with a great deal of caution in patients with decompensated liver disease, as one may precipitate the untimely demise of the patient even though viral replication is decreased. One of the patients in the IFN study in fact did have decompensation after prednisone therapy, which subsequently led, a couple of months later, to a variceal haemorrhage. In summary, in treating hepatitis B viral infection, no single agent is totally effective and perhaps the combination of suppressing viral replication and augmenting the immune system is the optimal way to eradicate the virus. At present, an adequate response is found in only about 30-40% of patients even with 'optimal' therapy.

Improvement of liver fibrosis in chronic hepatitis C patients treated with natural interferon alpha.

Hiramatsu N; Hayashi N; Kasahara A; Hagiwara H; Takehara T; Haruna Y; Naito M; Fusamoto H; Kamada T
J Hepatol (Denmark) Feb 1995, 22 (2) p135-42

To investigate the histological change (change of liver fibrosis) produced by the anti-viral effect of interferon on hepatitis C virus, 40 patients with chronic hepatitis C treated with natural interferon alpha were divided according to the existence of viremia at the end of treatment and 6 months after the end of treatment. The condition of liver fibrosis was scored numerically with a new "hepatic fibrosis score" which is sensitive to more subtle changes than Knodell's fibrosis score. Each portal zone was evaluated separately. End-of-treatment biopsy for the HCV RNA-negative group (negative for HCV RNA at the end of treatment) showed a significant improvement of the "hepatic fibrosis score" as well as the alleviation of necrosis and inflammation. At the end of treatment and 6 months after that, serum procollagen type III peptide levels and serum type IV collagen-7s levels had also decreased significantly in the HCV RNA-negative group. The present study showed that treatment with interferon alpha could alleviate fibrosis in addition to necrosis and inflammation.

Diagnosis and treatment of the major hepatotropic viruses.

Kiyasu PK; Caldwell SH
Am J Med Sci (United States) Oct 1993, 306 (4) p248-61

The hepatotropic viruses currently include hepatitis A, B, C, D, and E, and are associated with a spectrum of acute and chronic liver disease syndromes. The epidemiology and natural history of each are discussed, with emphasis on uncommon or newly recognized clinical presentations. The serodiagnosis of hepatitis A, B, and D is well established; the serodiagnosis of hepatitis C and E continues to evolve as serologic and virologic assays become refined. Hepatitis A and E only cause acute liver injury; current medical approaches therefore focus on vaccination strategies. Hepatitis B, C, and D can cause both acute and chronic liver injury. Sequelae of chronic liver disease, including portal hypertension and hepatocellular carcinoma, are not uncommon. Medical therapy of resulting chronic liver disease currently consists of interferon, though other anti-viral strategies are being explored. Advanced chronic liver disease due to hepatitis B, C, or D can be treated by orthotopic liver transplantation, but viral recurrence is near uniform and can be problematic. Further study of the hepatotropic viruses at the molecular biologic, epidemiologic, and clinical levels will continue to provide greater insight into the diagnosis and management of their associated clinical syndromes. (161 Refs.)

Treatment of chronic viral hepatitis.

Dusheiko GM; Zuckerman AJ
J Antimicrob Chemother (England) Jul 1993, 32 Suppl A p107-20

A substantial number of anti-viral compounds have been evaluated for the treatment of patients with chronic viral hepatitis. A few of these compounds have now achieved clinical applicability. alpha-Interferon is the most widely studied and remains the main treatment for chronic hepatitis B and C. Unfortunately in both these conditions only a minority of patients respond to interferon therapy, although the response can be complete in some patients. Some parameters have been identified which assist in the selection of patients for treatment. Several other cytokines, including thymosin, have been evaluated for the treatment of chronic hepatitis B. There are a number of promising new nucleosides which may inhibit hepatitis B virus and their action is being studied. Relapse rates are unknown however with these compounds. Ribavirin, a guanosine analogue, is also efficacious in treating a proportion of patients with chronic hepatitis C and the drug may be useful in treating patients with cirrhosis or patients who have an

[Mechanisms of the effect of interferon (IFN) therapy in patients with type B and C chronic hepatitis]

Karino Y

Hokkaido Igaku Zasshi (Japan) May 1993, 68 (3) p297-309

The relationship between 2', 5'-oligoadenylate synthetase (2-5AS) and HLA class I antigen in the hepatocyte of patients with type B or type C chronic hepatitis with and without interferon (IFN) therapy was investigated. The expression of HLA class I antigen of hepatocytes of biopsied specimen and PBL HLA class I antigen expression showed relevancy. Then, the HLA antigen expression of peripheral blood lymphocyte (PBL) and the 2-5AS activity of peripheral blood mononuclear cell (PBMC) were analyzed. In patients with type B or type C hepatitis, the mean activity of PBMC 2-5AS was significantly higher than that of healthy controls. Also the HLA class I antigen expression of PBL was significantly intense in patients with type B or type C hepatitis compared with healthy controls. In the acute exacerbated phase of type B chronic hepatitis, the HLA class I antigen expression of PBL and 2-5AS activity of PBMC increased along with elevation of serum GPT and then decreased with the remission of serum GPT. These results suggest that endogenously produced IFN leads the lysis of hepatocyte infected with hepatitis B virus (HBV) by cytotoxic T cells, and the restriction of HBV replication by activation of the 2-5A system simultaneously, and then leads the elimination of HBV. The activity of PBMC 2-5AS and the expression of PBL HLA class I antigen increased significantly during IFN therapy. In type B chronic hepatitis, the effective cases showed relatively high activity of serum 2-5AS compared with the non-effective cases. On the other hand, there were no significant differences in PBL HLA class I antigen expression between effective cases and non-effective cases. In type C chronic hepatitis, most patients with type III and type IV HCV genotype showed disappearance of HCV-RNA regardless of serum 2-5AS activity. In patients with type II HCV genotype, the serum 2-5AS activity was related to the antiviral effect of IFN therapy.

A pilot study of ribavirin therapy for recurrent hepatitis C virus infection after liver transplantation.

Cattral MS; Krajden M; Wanless IR; Rezig M; Cameron R; Greig PD; Chung SW; Levy GA

Transplantation (United States) May 27 1996, 61 (10) p1483-8

Ribavirin is a guanosine analogue that normalizes serum liver enzymes in most nontransplant patients with chronic hepatitis C virus (HCV) infection. We conducted an uncontrolled pilot study of ribavirin in 9 liver transplantation recipients that had persistently elevated liver enzymes, active hepatitis by liver biopsy, and HCV RNA in serum by polymerase chain reaction. Ribavirin was given orally at dosages of 800-1200 mg per day for 3 mo. All 9 patients promptly responded to ribavirin: mean (+/- SD) ALT decreased from 392 +/- 377 IU/L immediately before treatment to 199 +/- 185 and 68 +/- 37 IU/L after 1 and 12 weeks of treatment, respectively, complete normalization of enzymes occurred in 4 patients. None of the patients cleared the virus from their serum during therapy, and biochemical relapse occurred in all patients 4 +/- 4.2 weeks after cessation of therapy. The hepatitis activity index of liver biopsy specimens obtained before and at the cessation of therapy was similar. Ribavirin treatment was resumed in 4 patients because of increasing fatigue (2 patients), rising bilirubin (3), or increasing necroinflammation on liver biopsy (2); the biochemical response to the second course of therapy was similar to the first course in all 4 patients. Ribavirin caused reversible hemolysis in all patients, including symptomatic anemia in 3 patients that resolved after reduction of drug dosage. These results suggest that ribavirin may be of benefit in the treatment of HCV infection after liver transplantation. Further studies are needed to determine the optimal dosage and duration of therapy.

Ribavirin as therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial.

Di Bisceglie AM; Conjeevaram HS; Fried MW; Sallie R; Park Y; Yurdaydin C;

Ann Intern Med (United States) Dec 15 1995, 123 (12) p897-903

OBJECTIVE: To evaluate ribavirin, an oral antiviral agent, as therapy for chronic hepatitis C.

DESIGN: Randomized, double-blind, placebo-controlled study.

SETTING: Clinical Center of the National Institutes of Health, a tertiary referral research hospital.

PATIENTS: 29 patients with chronic hepatitis C who received oral ribavirin (600 mg twice daily) for 12 months and 29 controls with chronic hepatitis C who received placebo for 12 months.

MEASUREMENTS: Effects of therapy were evaluated by measuring serum aminotransferase and hepatitis C virus (HCV) RNA levels before, during, and for 6 months after therapy and by histologic examination of liver specimens before and at the end of treatment.

RESULTS: Patients treated with ribavirin had a prompt decrease in serum aminotransferase levels (54% overall) compared with levels before treatment and levels in controls (5% decrease). Serum aminotransferase levels became normal or nearly normal in 10 patients treated with ribavirin (35% [95% CI, 18% to 54%]) but in no controls (0% [CI, 0% to 12%]). Aminotransferase levels remained normal in only 2 patients after ribavirin therapy was discontinued (7% [CI, 1% to 23%]). Serum HCV RNA levels did not change during or after therapy. Liver biopsy specimens showed a decrease in hepatic inflammation and necrosis among ribavirin-treated patients whose aminotransferase levels became normal.

CONCLUSIONS: Ribavirin has beneficial effects on serum aminotransferase levels and histologic findings in the liver in patients with chronic hepatitis C, but these effects are not accompanied by changes in HCV RNA levels and are not sustained when ribavirin therapy is discontinued. Thus, ribavirin alone for periods as long as 12 months is unlikely to be of value as therapy for chronic hepatitis C.

Treatment with ribavirin+alpha interferon in HCV chronic active hepatitis non-responders to interferon alone: preliminary results.

Scotto G; Ferrara S; Mangano A; Conte PE
J Chemother (Italy) Feb 1995, 7 (1) p58-61

Alpha interferon (IFN-alpha) represents the best therapy for HCV active chronic hepatitis, but only 25% of treated patients achieve a complete recovery. Several attempts have been made to increase this percentage. The objective of our study is to verify whether the combination ribavirin (R)+ IFN-alpha can lead to positive results in non-responders to treatment with IFN-alpha alone. The preliminary results for 5 subjects, all non-responders to IFN, treated with R+ IFN for 60 days and then IFN alone for 4 months more show that during the R+IFN treatment, 2 subjects presented a reduction in transaminase; a month after the suspension of R, ALT returned to pre-treatment values. The results are preliminary but we can say that this combination in the proposed doses and times in these subjects, cannot be considered adequate to modify the natural course of this disease.

Combined treatment with interferon alpha-2b and ribavirin for chronic hepatitis C in patients with a previous non-response or non-sustained response to interferon alone.

Schvarcz R; Yun ZB; Sonnerborg A; Weiland O
J Med Virol (United States) May 1995, 46 (1) p43-7

Ten patients with chronic hepatitis C, six of whom had not responded and four of whom had responded in a non-sustained fashion to interferon-alpha treatment alone, were given interferon alpha-2b and ribavirin in combination during 24 weeks. Interferon alpha-2b was given subcutaneously, at a dose of 3 MU thrice weekly, together with ribavirin orally, at a dose of 1,000-1,200 mg/day. All four patients with a prior non-sustained response to interferon alone had normal alanine aminotransferase (ALT) levels at the end of treatment as well as during follow-up (> or = 24 weeks post treatment). Furthermore, all four lost serum HCV-RNA at the end of treatment and three continued to be negative during follow-up. Among patients with a prior non-response to interferon alone three of six had normal ALT levels at the end of treatment and one at follow-up. Two of six became HCV-RNA negative at cessation of treatment, one of whom was negative also at follow-up. All former non-sustained responders and one of six non-responder patients thus showed a sustained biochemical response with eradication of HCV-RNA from serum in all cases but one. It is concluded that combination therapy with interferon alpha-2b and ribavirin offers a chance of sustained biochemical response with eradication of the viremia in patients who have not shown a persistent response to interferon-alpha alone.

Increase in hepatic iron stores following prolonged therapy with ribavirin in patients with chronic hepatitis C.

Di Bisceglie AM; Bacon BR; Kleiner DE; Hoofnagle JH
Liver Diseases Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Md 20892.
J Hepatol (Denmark) Dec 1994, 21 (6) p1109-12

Ribavirin, an oral nucleoside analogue being evaluated as therapy for chronic hepatitis C, is associated with hemolysis. Other hemolytic conditions are known to be associated with accumulation of iron within the liver. We therefore examined hepatic iron stores before and after 6 to 12 months of therapy with ribavirin in 15 patients with chronic hepatitis C. Although there were no significant changes in serum iron or ferritin levels, hepatic iron staining increased in almost all patients. Using a ranking system to quantitate the amount of hepatic iron staining, we found that the mean rank increased from 3.9 to 8.5 after therapy ($p < 0.01$). In six patients in whom hepatic tissue was available for determination of hepatic iron, concentrations also increased in all cases from a mean of 826 to 1857 micrograms/g dry weight ($p < 0.01$). The average rate of iron accumulation in these six patients was approximately 1500 micrograms/g per year. Thus hepatic iron concentrations might enter the range clearly associated with hepatic fibrosis after approximately 15 years of continuous therapy.

Therapy for chronic hepatitis C.

Davis GL; Lau JY; Lim HL

Gastroenterol Clin North Am (United States) Sep 1994, 23 (3) p603-13

Hepatitis C is the silent epidemic of the 1970s and 1980s. Interferon alfa is currently the only effective treatment. Enthusiasm for interferon therapy must be tempered because advanced disease usually requires years or even decades to develop and does not occur in all patients. Few patients with chronic hepatitis C derive long-term improvement from a single 6-month course of interferon therapy. Most initial responders relapse and require long-term interferon treatment to suppress the virus. Obviously, the initial goals and expectations for interferon therapy require rethinking. Therapy should not be undertaken by physician or patient with the idea that therapy will be limited to 6 months. The most appropriate goal of therapy now appears to be the long-term control of the biochemical, virologic, and histologic activity of the disease. Unfortunately, the most effective therapeutic regimen for achieving this goal is not yet known and will require continued clinical research. (52 Refs.)

Treatment of chronic viral hepatitis.

Marcellin P; Benhamou JP

Baillieres Clin Gastroenterol (England) Jun 1994, 8 (2) p233-53

Recent advances have been made in the treatment of chronic viral hepatitis, mainly with recombinant interferon (IFN) alpha. However, the present treatment of chronic viral hepatitis is not entirely satisfactory because the efficacy is inconstant and/or incomplete. In chronic hepatitis B IFN-alpha induces a sustained interruption of hepatitis B virus (HBV) replication, with a HBeAg to anti-HBe seroconversion in about 30% of patients. Patients most likely to respond are those with no immunosuppression, HBV infection acquired during adulthood or active liver disease with low HBV replication. Responders usually show a significant decrease in serum HBV DNA levels during the first 2 months of therapy, followed by a significant increase in the level of aminotransferases. New nucleoside analogues might be useful in combination with IFN-alpha in the treatment of those who do not respond to IFN therapy. In chronic hepatitis B-D, the rate of sustained response to IFN-alpha therapy is low. To be effective, IFN-alpha must be used at a high dosage (9-10 mega units) with a long duration (1 year). In chronic hepatitis C, IFN-alpha at a dosage of 3 mega units over 6 months, induces a sustained response in about 20% of patients. A higher dosage of IFN (5-10 mega units) and a longer duration of treatment increases the rate of sustained response but is associated with poor tolerance. Non-responders to a first course of IFN do not respond to a second course of treatment. In patients who respond but relapse after treatment, the rate of sustained response after a second course of IFN needs to be assessed. Ribavirin, which has a significant antiviral effect on hepatitis C virus, might be useful in combination with IFN-alpha. At the dosage (3-6 mega units) usually used, IFN-alpha is relatively well tolerated. In about 10% of the patients therapy is interrupted, mainly because of severe fatigue, thyroid dysfunction or depression. (84 Refs.)

Elevated serum iron predicts poorresponse to interferon treatment in patients with chronic HCV infection.

Arber N; Moshkowitz M; Konikoff F; Halpern Z; Hallak A; Santo M; Tiomny E ; Baratz M; Gilat T

Dig Dis Sci (United States) Nov 1995, 40 (11) p2431-3

To date, there are no firm clinical, demographic, biochemical, serologic, or histologic features predicting which patients with chronic hepatitis C are more likely to respond to therapy with interferon-alpha. Serum iron, total iron-binding capacity, transferrin saturation, and ferritin were measured in the fasting state. The amount of stainable iron in liver biopsy specimens was evaluated histochemically as well. All patients received subcutaneous recombinant human IFN-alpha 2a three million units thrice weekly by self-administration. Eleven of 13 (84%) responders had low to normal serum iron levels as compared to one of 26 (4%)

nonresponders ($P < 0.001$). The serum transferrin was similar in both groups, but iron saturation was significantly lower in responders ($30 \pm 10\%$) than in nonresponders ($53 \pm 12\%$) ($P < 0.001$). Serum ferritin and hepatic iron content were higher in nonresponders (NS). It is suggested that increased serum iron and transferrin saturation blunt the action of interferon, as they have opposite effects on the immune system. Iron overload can thus lead to a poor response to interferon. It remains to be seen whether reducing iron overload will improve the response to interferon therapy.

Distribution of iron in the liver predicts the response of chronic hepatitis C infection to interferon therapy

Barton AL; Banner BF; Cable EE; Bonkovsky HL
Am J Clin Pathol (United States) Apr 1995, 103 (4) p419-24
[published erratum appears in Am J Clin Pathol 1995 Aug;104(2):232]

Recent evidence suggests that patients with chronic hepatitis C virus (CHCV) who respond to interferon-alpha (IFN) therapy have a lower hepatic iron concentration than those who do not. The object of this study was to assess the concentration and distribution of iron in liver biopsies from 15 patients with CHCV seen at the authors' medical center between June 1992 and March 1993. Patients with complete response to IFN were compared to those with non-complete response with respect to quantitative hepatic iron concentration, serum iron indices, and a detailed analysis of histologic features of hematoxylin-and-eosin and iron-stained pre-IFN biopsies. Patients with non-complete response had significantly higher scores for stainable iron in sinusoidal cells ($P = .02$) and portal tracts ($P = .05$) than did patients with complete response. Total hepatic iron scores, mean quantitative hepatic iron, and mean serum ferritin were higher in patients with noncomplete response, but the differences were not significant. In conclusion, iron deposition in sinusoidal cells and portal tracts is significantly less frequent in patients with complete response to IFN than in those with poor or no response, and may be a useful, objective predictor of response to IFN therapy.

Increased serum iron and iron saturation without liver iron accumulation distinguish chronic hepatitis C from other chronic liver diseases.

Arber N; Konikoff FM; Moshkowitz M; Baratz M; Hallak A; Santo M; Halpern
Dig Dis Sci (United States) Dec 1994, 39 (12) p2656-9

One hundred twenty-three patients with chronic liver diseases of various etiologies were evaluated for their iron status. The patients were divided into four distinct groups: chronic hepatitis C (63), chronic hepatitis B (14), B + C (3) and nonviral chronic liver diseases (43). In 107 patients (87%) the chronic liver disease was confirmed by biopsy. Mean serum iron (\pm SD) levels in the above four groups were: 166 ± 62 , 103 ± 52 , 142 ± 48 , and 115 micrograms/dl; iron-binding capacity was 346 ± 80 , 325 ± 72 , 297 ± 27 , and 374 ± 75 micrograms/dl, and iron saturation 50 ± 18 , 32 ± 16 , 48 ± 16 , and $28 \pm 10\%$, respectively. Serum ferritin, increased in all four groups, was highest in HCV; however, no evidence of hepatic iron accumulation could be found in any of the patients. There were no significant differences in liver function parameters measured in the four groups. We conclude that serum iron, iron saturation, and ferritin are increased in patients with hepatitis C in comparison to hepatitis B or other nonviral, nonhemochromatotic liver diseases. The increased iron status in hepatitis C patients is not manifested by increased liver iron. Awareness of these distinct features of chronic hepatitis C is essential in the diagnosis and treatment of chronic liver diseases.

Response related factors in recombinant interferon alfa-2b treatment of chronic hepatitis C.

Perez R; Pravia R; Linares A; Rodriguez M; Lombrana JL; Suarez A; Riestra
Gut (England) 1993, 34 (2 Suppl) pS139-40

In an analysis of the clinical and laboratory variables that can influence the response to interferon alfa-2b treatment, 48 patients with chronic hepatitis C virus infection received interferon 5 million units (MU) subcutaneously three times weekly for eight weeks followed by 3 MU three times weekly for seven months. Response related factors on univariate analysis were found to be age > 40 years, non-parenteral source of infection, pretreatment positive antinuclear antibodies (ANA), cirrhosis, and high serum iron, ferritin, gamma glutamyl transferase, and IgM. An independent predictive value (multivariate analysis) was also found for cirrhosis, ANA, serum iron, and ferritin. A baseline aspartate aminotransferase/alanine aminotransferase ratio of 0.5 and a striking increase during interferon treatment were associated with a complete response.

Measurements of iron status in patients with chronic hepatitis

Eighty patients with chronic viral hepatitis were screened for evidence of iron overload. Elevated serum iron values were noted in 36% of cases; serum ferritin values were above normal in 30% of men and 8% of women. Twenty-eight additional patients with chronic hepatitis for whom liver tissue was available for determination of iron content were evaluated to study the significance of iron overload in association with chronic hepatitis. Although 46% had elevated serum iron, ferritin, or transferrin-saturation levels, the hepatic iron concentration was elevated in only four cases, and the hepatic iron index was in the range for hereditary hemochromatosis (greater than 2.0) in only two of these. Serum aspartate aminotransferase activities correlated with serum ferritin levels in these patients, suggesting that ferritin and iron levels were increased in serum because of their release from hepatocellular stores associated with necrosis. Thus, in patients with chronic hepatitis in whom hereditary hemochromatosis is suspected, a liver biopsy should be performed with quantitation of hepatic iron and calculation of the hepatic iron index to confirm the diagnosis.

[Effect of green tea on iron absorption in elderly patients with iron deficiency anemia]

Kubota K; Sakurai T; Nakazato K; Morita T; Shirakura T
Department of Medicine, Kusatsu Branch Hospital, Gunma University School of Medicine.
Nippon Ronen Igakkai Zasshi (Japan) Sep 1990, 27 (5) p555-8

The effect of green tea on iron absorption from tablets containing sodium ferrous citrate was investigated in four elderly patients with iron deficiency anemia and in eleven normal elderly subjects. In both groups, the serum iron level reached a maximum value from 2 to 4 hours after taking iron tablets and returned to the baseline value after 24 hours. No inhibitory effect of green tea on iron absorption was recognized.

[Current knowledge in the treatment of chronic hepatitis C]

Pirotte J
Service d'Hepato-Gastroenterologie, Universite de Liege.
Rev Med Liege (Belgium) Dec 1995, 50 (12) p501-4, (29 Refs.)

No abstract.