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December 21, 1993

Dear Editor:

Thank you for your interest in abstracts on ribavirin and hepatitis C presented at the National Liver Association meeting November 4-7, 1993 in Chicago.

For your background and files, please find these abstracts enclosed, as well as a summary of them along with a background sheet on hepatitis C. Earlier studies

published in Lancet and Hepatology on ribavirin and hepatitis C are also enclosed. Ribavirin is not yet approved for this indication by the FDA.

Should you have any questions, please feel free to call.

Sincerely,

Jack Sholl
Senior Vice President
Public Relations

enc.

RIBAVIRIN/HEPATITIS CLINICAL ABSTRACTS SUMMARY

* Preliminary results from a study conducted at the National Institutes of Health's Liver Unit found that capsules of ICN Pharmaceutical Inc.'s antiviral drug ribavirin (Virazole) may be useful in treating hepatitis C. Ribavirin was demonstrated to have significant effects on key clinical parameters. The double blind, placebo-controlled study involves 58 patients using ribavirin to treat chronic hepatitis C infection. In an abstract published in Hepatology (Vol. 18, No. 4, pt. 2, 1993) NIH investigators said initial preliminary results of 32 patients showed that in 16 patients "...prolonged ribavirin therapy was associated with significant improvement in serum ALT levels despite unchanged serum HCV RNA levels) and in hepatic lobular necrosis." The average decrease of liver enzymes in patients taking ribavirin was 47 percent. The drug was well tolerated; slight, reversible anemia being the only systematic finding, together with a slight decrease in T-lymphocytes. Full results await publication.

* A separate study involving 60 patients conducted in Taiwan was designed to compare the efficacy of combined interferon and ribavirin (Virazole) therapies versus interferon therapy alone. Among the group receiving combination therapy, 78 percent of patients had liver enzyme levels return to normal (they were initially at least two times normal), and the change was sustained for up to five months. In the group that received interferon alone, only 33 percent of patients had liver enzyme levels return to normal (from at least two times normal), and all interferon patients had a relapse of elevated liver enzyme levels one month after the cessation of the drug. The combination of interferon and ribavirin (Virazole) was well tolerated.

* A study conducted in Italy found that the combination of interferon and ribavirin (Virazole) may benefit patients who were previously resistant to interferon alone, or who had relapsed after treatment with interferon. Twenty patients, ten non-respondents and ten patients relapsing after treatment with interferon, were randomized to either Virazole combined with interferon, or interferon. After six months of treatment and another six months of follow-up, the combination induced sustained normalization in 60 percent of patients relapsing after interferon, and 40 percent sustained normalization in non-responders to interferon. The sustained normalization of ALT levels was always accompanied by sustained loss of viremia. No sustained responses were seen in the patients receiving interferon only. The combination of Virazole and interferon was well tolerated.

(Virazole is authorized in the U.S. in aerosol form for the treatment of of infants hospitalized with severe lower respiratory tract infection caused by respiratory syncytial virus. Any other indication or reference in the U.S. is investigational. Labeling is attached).

FACTS ABOUT HEPATITIS C

* According to the American Liver Foundation, hepatitis C is the second most prevalent form of hepatitis in the United States. Hepatitis C is a slowly progressive liver disease that often leads to inflammation of the liver, cirrhosis, and liver cancer. About 8 to 10 thousand deaths per year can be attributed to the disease.

* According to the Centers for Disease Control, 150,000 people are infected with hepatitis C annually. An estimated 1.8 million Americans are already infected. There are roughly 275,000 cases of active chronic (symptomatic) hepatitis C.

* Hepatitis C was first identified in 1987, and the first diagnostic test designed to identify people with the disease was available in 1990. Before then it was referred to as non-A, non-B hepatitis.

* Most people infected don't develop overt symptoms right away but remain infectious. The disease is often dormant for decades, making hepatitis C an invisible epidemic.

* Virtually all individuals infected with hepatitis C will develop active chronic hepatitis disease (exhibiting some symptoms) or will be chronic carriers of the virus. Once infected, most patients remain infected for life.

* It is generally believed that hepatitis C is transmitted through blood-to-blood contact: blood transfusions and/or intravenous drug use. There may also exist several unknown modes of transmission.

* The hepatitis C virus differs from other viruses that cause hepatitis, such as hepatitis A and hepatitis B. Unlike hepatitis C, hepatitis A is transmitted through food and water contaminated with fecal matter. Similar to hepatitis C, hepatitis B is transmitted through blood-to-blood contact or contact with other bodily fluids. Hepatitis B accounts for the majority of hepatitis cases in the United States.

WHO IS AT RISK?

* The Centers for Disease Control estimate that hepatitis C develops in 1 to 5 percent of people who received multiple blood transfusions.

* It is estimated that up to 80 percent of intravenous drug users admitted to hospital emergency rooms are infected with hepatitis C.

RIBAVIRIN TREATMENT FOR CHRONIC HEPATITIS C

Olle Reichard Jan Andersson Robert Schvarcz
Ola Weiland

We evaluated oral ribavirin as therapy for chronic hepatitis C infection in a pilot study including 10 patients. Patients (7 men, 3 women; mean age 40 years, range 23-54) all had biopsy-proven chronic non-A, non-B hepatitis and were repeatedly positive for antibodies to hepatitis C virus. Treatment was with oral ribavirin 1000-1200 mg per day in two divided doses for 12 weeks. The median serum alanine aminotransferase concentration for all patients at enrollment was 3.15 ukat/l (range 1.22-7.79) and decreased significantly ($p<0.005$) to 1.25 ukat/l (0.78-2.04) after 12 weeks of treatment. Within 6 weeks of the end of treatment the median serum alanine aminotransferase

concentration was not significantly different from that before treatment. Side-effects were mild and fully reversible after cessation of therapy. We conclude that ribavirin is the first drug to offer a potentially effective oral treatment for chronic hepatitis C. It should be further evaluated in controlled trials, possibly in combination with interferon alpha.

Lancet 1991;337;1058-61.

INTRODUCTION

Hepatitis C virus, an RNA virus similar to the flavivirus and perstivirus families, has been shown to be the most important setiologic agent of chronic non-A, non-B hepatitis.(1),(2) Prospective studies indicate that non-A, non-B hepatitis will develop in about 1-5% of multiple transfused individuals in the industrialised world.(3),(4) Chronic liver disease will develop in about half these patients, of whom some 20% will progress to liver cirrhosis.(3)-(5)

Interferon alpha (IFN alpha) is the only treatment for hepatitis C that has been evaluated thoroughly. Serum alanine aminotransferase (ALT) concentrations return to normal in about 50% of patients receiving long-term treatment with subcutaneous IFN alpha.(6),(7) However, after treatment ceases, ALT concentrations remain normal in only 10-20% of patients.(6),(7)

ADDRESSES: Departments of Infectious Diseases, Karolinska Institute, Danderyds Hospital (O. Relchard, MD, J. Andersson, MD, PhD), and Roslagstulls Hospital (R. Schvarcz, MD, O. Weiland, MD, PhD), Stockholm, Sweden, Correspondence to Dr. Ola Weiland, Department of Infectious Diseases, Karolinska Institute, Roslagstulls Hospital, Box 5651, 114 89, Stockholm, Sweden.

[CHART]

FIG 1 -- CHANGE IN MEDIAN ALT CONCENTRATIONS IN 10 PATIENTS TREATED WITH RIBAVIRIN.

The box shows the 25th through 75th percentile, the bar within the box the 50th percentile, the upper and lower bars the 90th and 10th percentile, respectively. 5-12 months before treatment (II), 3-10 weeks before treatment (I): *p < 0.005, **not significant, Wilcoxon signed rank test.

Ribavirin (1-B-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a non-interferon-inducing nucleotide analogue with a broad spectrum of activity against RNA and DNA viruses, including those from the flavivirus family.(8)(9) The drug has often been used as an aerosol to treat respiratory syncytial virus infections, but has not been used extensively in other viral infections because of reports of teratogenic and/or embryolethal effects in rodents and rabbits,(10) although no teratogenicity has been seen in baboons.(10) It is not thought to have mutagenic or carcinogenic effects.(11) Trials of oral ribavirin therapy have been done in patients infected with human immunodeficiency virus,(12) hepatitis B virus,(13) and Lassa fever virus.(14) We therefore designed a pilot study to evaluate the clinical benefits and side effects of oral ribavirin treatment in patients with chronic hepatitis C.

PATIENTS AND METHODS

Patients were entered into the trial if they had biopsy finding

consistent with a diagnosis of chronic non-A, non-B hepatitis and were repeatedly positive for antibodies to hepatitis C virus by enzyme-linked immunosorbent assay ('Ortho-HCV', Ortho Diagnostic Systems). 7 men and 3 women - -- mean age 40 years (range 23-54) -- met the criteria and were included in the study. 4 patients had acquired hepatitis from intravenous drug abuse, 5 from blood transfusions, and 1 had no known source of infection. All patients had raised serum ALT concentrations for a minimum of 12 months before study entry. No patients had markers for hepatitis B virus infection or human immunodeficiency virus infection, or alcoholic, drug-related, autoimmune, or metabolic liver disease, and none had received antiviral or immunomodulatory therapy within the 6 months before study entry. Prestudy liver biopsy showed that half the patients had chronic active hepatitis (CAH) and half had chronic persistent hepatitis (CPH). The trial was approved by the

[CHART]

FIG 2 -- CHANGE IN ALT CONCENTRATIONS FOR INDIVIDUAL PATIENTS WITH CAH (A) AND CPH (B) BEFORE, DURING, AND AFTER TREATMENT WITH RIBAVIRIN.

5-12 months before treatment (II), 3-10 weeks before treatment (I)

ethical committee at the Karolinska Institute, and all patients gave informed verbal consent.

All patients were treated with two doses per day of oral ribavirin (ICN Pharmaceuticals, California, USA) for 12 weeks at 1000 mg/day for patients weighing 55-75 kg and 1200 mg/day for patients weighing more than 75 kg. Side effects were monitored by questioning and examination. Haemoglobin, white cells, platelets, differential blood cell counts including granulocyte counts, serum uric acid, and serum creatininc were measured before the start of therapy and at weeks 1, 3, 5, 7, 9, and 12 during treatment and weeks 1, 2, 6, and 12 post-treatment. Serum albumin was determined before treatment started and 12 weeks after treatment finished. Statistical analyses were done with the Wilcoxon signed rank test.

RESULTS

Biochemical response to ribavirin

Serum ALT concentrations decreased in all patients during ribavirin therapy, but increased to pretreatment concentrations after treatment coded (fig 1, fig 2). The median serum ALT concentration for all patients at enrolment was 3.15 ukat/l (range 1.22-7.79) and decreased significantly ($p<0.005$) to 1.25 ukat/l (range 0.78-2.04) by the end of treatment. The median ALT concentration 6 weeks after cessation of treatment (2.48 ukat/l, range 0.7-5.26) was not significantly different from the pretreatment value (fig 1). Between weeks 0 and 12 of ribavirin therapy, median ALT concentrations decreased significantly from 3.28 ukat/l (2.28-7.79) to 1.32 ukat/l (0.78-2.04) in patients with CAH ($p<0.04$), and from 1.78 ukat/l (1.22-3.68) to 1.0 ukat/l (0.9-1.55) in patients with CPH ($p<0.04$). 6 weeks after cessation of treatment, median serum ALT concentrations were 2.32 ukat/l (1.71-5.26) and 2.64 ukat/l (0.7-3.42) for patients with CAH and CPH, respectively, and not significantly different from pretreatment concentrations.

The biochemical findings before, during, and after ribavirin treatment are shown in the table. A decrease in mean serum haemoglobin during treatment was seen. The fall was most notable from treatment weeks 1-5 after which haemoglobin concentration stabilized. Serum uric acid concentrations rose slightly during treatment, but no changes were seen in white blood cell and differential blood cell counts, platelet count, serum albumin, and prothrombin time (table). Haemoglobin and serum uric acid became normal 6 weeks after treatment.

Side effects

Adverse reactions were mild and fully reversible after cessation of therapy, 6 of the 10 patients had no side effects, 1 patient had myalgia, 1 had nausea, 1 had fatigue not necessitating dose changes, and 1 patient experienced itching on the last day of treatment and a few days thereafter. The same patient's haemoglobin fell from 156 g/l at week 0 to 117 g/l at week 12, after which haemoglobin rose spontaneously to pretreatment concentrations.

DISCUSSION

Although hepatitis C virus infection is usually a subclinical disease in its acute phase, its propensity to progress to chronic hepatitis, cirrhosis, and, possibly, hepatocellular carcinoma means that effective treatment must be sought. The major drawbacks of IFN alpha therapy are prolonged parenteral treatment schedules and the fact that most patients who respond relapse after treatment withdrawal.(6,7)

Since oral ribavirin treatment is tolerated in patients with other virus infections,(12-14) it seemed reasonable to try this therapy in patients with chronic hepatitis C infection. In our study, serum ALT concentrations were significantly reduced during oral ribavirin therapy of 10 patients with chronic hepatitic C virus infection and this effect was probably caused by the antiviral properties of ribavirin.(8,9) Ribavirin treatment was well tolerated with few side effects (table). The favourable effect on serum ALT concentrations was, although not sustained after treatment cessation, similar to that seen with IFN alpha therapy.(6,7) Ribavirin is, however, the first drug to offer a potentially effective oral treatment for chronic hepatitis C virus infection.

This pilot study seems to demonstrate an antiviral effect of ribavirin in individuals with chronic hepatitis C virus infection, even if the mechanism of action is not known. Combination therapy with IFN alpha may cure individuals of chronic hepatitis C virus infection, and this combination should be evaluated in future trials.

MEAN OF MEDIAN (RANGE) LABORATORY FINDINGS IN 10 PATIENTS WITH CHRONIC HEPATITIS C TREATED WITH RIBAVIRIN

<TABLE>
<CAPTION>

		WEEKS FROM START OF TREATMENT			
-	PRE-TREATMENT	5	12*	18	24
<S>	<C>	<C>	<C>	<C>	<C>
Median ALT+ (ukat/l)	3.15 (1.22-7.79)	1.5 (0.72-2.65)	1.25 (0.78-2.04)	2.48 (0.70-5.26)	2.92 (1.21-5.86)
Mean haemoblobulin (g/l)	150 (133-172)	134 (117-159)	132 (110-157)	149 (133-171)	150 (121-175)
Mean bilirubin (mmol/l)	11-2 (6-16)	10 (6-26)	13 (7-21)	9 (1-22)	11 (2-19)
Mean uric acid (mmol/l)	286 (201-372)	301 (185-447)	320 (261-465)	262 (167-364)	248 (144-356)
Mean white blood cell count (x 10/l)	6.1 (4.4-8.0)	5.7 (3.8-7.9)	5.0 (4-7.1)	5.5 (4.1-6.7)	5.4 (4.4-6.7)
Mean granulocyte count (x 10/l)	3.2 (1.9-4.5)	3.3 (1.9-5.5)	2.9 (2.1-4.5)	3.1 (1.8-4.4)	3.0 (2-4.2)
Mean platelet count (x 10/l)	245 (141-341)	272 (155-405)	257 (160-368)	245 (150-319)	225 (114-326)
Mean albumin (g/l)	41.7 (37-46)	..	41.1 (39-44)	..	42.7 (38-48)
Mean prothrombin	87	83	86	91	87

time(s) (68-130) (70-103) (66-123) (71-126) (72-122)
</TABLE>
* End of treatment.
+ Upper limit of normal=0.7 ukat/l.

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Consent of publication has not been received from The Lancet as of the

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A PILOT STUDY OF RIBAVIRIN THERAPY FOR CHRONIC HEPATITIS C

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A PILOT STUDY OF RIBAVIRIN THERAPY FOR CHRONIC HEPATITIS C

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INTERFERON-ALPHA THERAPY IS OF PROVEN EFFICACY IN CHRONIC HEPATITIS C, BUT IT IS NOT UNIVERSALLY EFFECTIVE AND MAY BE ASSOCIATED WITH INTOLERABLE SIDE EFFECTS. RIBAVIRIN IS A NUCLEOSIDE ANALOG WITH A BROAD SPECTRUM OF ANTIVIRAL ACTION. WE CONDUCTED AN UNCONTROLLED PILOT STUDY OF RIBAVIRIN THERAPY IN 13 PATIENTS WITH CHRONIC HEPATITIS C. RIBAVIRIN WAS GIVEN FOR 6 MO, IN A DOSE THAT WAS INCREASED, AT 2-MO INTERVALS, FROM 600 MG TO 1,000 MG TO 1,200 MG/DAY. SERUM ALT LEVELS GRADUALLY DECREASED IN ALL 13 TREATED PATIENTS; THE MEAN PERCENTAGE OF DECREASE WAS 67% (FROM 210 U/L [RANGE = 109 TO 593] TO 63 U/L [RANGE = 22 TO 108 U/L]; P = 0.0006) AFTER 6 MO OF TREATMENT. SERUM AMINOTRANSFERASE LEVELS FELL TO THE NORMAL RANGE IN FOUR PATIENTS (31%). IN THE 3 TO 6 MO AFTER CESSATION OF RIBAVIRIN THERAPY, SERUM AMINOTRANSFERASE ACTIVITIES GRADUALLY ROSE TO NEAR PRE-TREATMENT LEVELS IN ALL BUT ONE PATIENT. THERAPY WAS ASSOCIATED WITH A SIGNIFICANT DECREASE IN THE GEOMETRIC MEAN TITER OF HEPATITIS C VIRUS RNA IN SERUM (1:1,981 VS. 1:199; P LESS THAN 0.02) ALTHOUGH NO PATIENTS LOST HEPATITIS C VIRUS RNA FROM SERUM DURING THERAPY. NO SIGNIFICANT IMPROVEMENT WAS SEEN IN LIVER HISTOLOGICAL APPEARANCE. RIBAVIRIN THERAPY RESULTED IN MILD, REVERSIBLE HEMOLYSIS; NO PATIENT EXHIBITED SYMPTOMATIC ANEMIA. THESE FINDINGS SUGGEST THAT RIBAVIRIN HAS A BENEFICIAL EFFECT IN PATIENTS WITH CHRONIC HEPATITIS C, ALTHOUGH FURTHER STUDIES ARE

NEEDED TO DETERMINE HOW RIBAVIRIN IS BEST USED. (HEPATOLOGY 1992;16:649-654.)

Chronic hepatitis C is typically an insidious and slowly progressive disease. In some patients, cirrhosis and even HCC develop (1-3). This disease is caused by chronic infection with the hepatitis C virus (HCV), which was recently identified as a single-stranded RNA virus. Specific tests are now available for detection of antibody to HCV (anti-HCV) and for the nucleic acid of the agent (4, 5). Recently interferon-alpha was shown to be effective in decreasing the level of hepatocellular injury and inflammation in patients with chronic hepatitis C (6, 7). Unfortunately, interferon is not universally effective, and its usefulness is often limited by side effects such as fatigue, depression, bone marrow suppression or autoimmune thyroid disease (8). It is clear that safer and more effective treatments that interfron for chronic hepatitis C should be sought.

Ribavirin (1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) is a nucleoside analog with a broad spectrum of antiviral activity against RNA viruses, including some agents that resemble HCV (9). We report the results of a preliminary study of 13 patients with chronic hepatitis C infection who underwent 6 mo of therapy with ribavirin.

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Received December 3, 1991; accepted April 28, 1992.
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31/1/39158

PATIENTS AND METHODS

Adult patients with chronic hepatitis C infection and anti-HCV in serum or histories of parenteral exposure to blood or blood products were eligible for this study. Patients were included if they had persistently elevated serum aminotransferase activities for at least 6 mo and the serum ALT level was at least twice the upper limit of the normal range on two separate occasions (at least 1 mo apart) before therapy. Only patients with compensated liver disease who had no other serious medical illnesses and no evidence of liver disease other than hepatitis C were included. Patients with HBsAg or antibody to human immunodeficiency virus (anti-HIV) in serum were excluded.

After evaluation and percutaneous liver biopsy, patients were given ribavirin (Viratek, Inc., Costa Mesa, CA) orally in two daily doses. The medication was given for 6 mo, starting at 600 mg/day and increasing after 2 mo to 1,000 mg/day. After another 2 mo, the dose of ribavirin was increased to 1,200 mg/day in those patients whose serum ALT values were not yet normal or near normal (less than 1.5 times the upper limit of normal). Compliance with therapy was monitored by means of patient diaries. Patients were examined and had blood samples taken weekly for the first month and then monthly for the duration of treatment and the following 6 mo. Thereafter, patients were evaluated at 3-mo intervals. On each occasion, blood was tested for complete blood counts; routine serum biochemical function tests, including those for serum aminotransferase activities, were also performed. Liver biopsy was repeated after 6 mo of treatment. Histological changes associated with treatment were assessed by two reviewers (CAA and AMD), who examined pretreatment and posttreatment liver biopsy samples under code.

Liver biopsy specimens were stained with hematoxylin and sosin and by Masson's trichrome method. The degrees of necroinflammatory change and portal-portal bridging were evaluated with the scale developed by Knodell et al. (10). In addition, all specimens were ranked from least to most severe current hepatic injury, as described previously (7). The degree of current hepatic injury was judged after assessment of the

Fig. 1. Mean percentage change in serum ALT values during and

after 6 mo of therapy with ribavirin.

degree of periportal (piecemeal) necrosis, portal inflammatory infiltrate, bridging and intralobular hepatocellular necrosis.

Initial serum samples were tested for anti-HCV by ELISA (HCV ELISA; Ortho Diagnostic Systems, Raritan, NJ). Serum samples taken at 3-mo intervals were tested for HCV RNA by the "double" polymerase chain reaction method with "nested" oligonucleotide primers from the highly conserved 5' noncoding region of the genome as previously described (11, 12). Each assay included two serum samples from healthy normal volunteers known to be negative for HCV RNA (as controls). The amount of HCV RNA detected was quantitated by performing serial 10-fold dilutions of extracted RNA before polymerase chain reaction and by estimating a titer of HCV RNA by end-point dilution. Anti-HIV was tested with an ELISA (Abbott Laboratories, North Chicago, IL), and HBsAg and antibody to HBcAg were tested by RIA (AUSRIA II and Corab; Abbott Laboratories).

The details of this treatment protocol were approved by the Institutional Clinical Research Subcommittee of the National Institute of Diabetes and Digestive and Kidney Diseases; all patients gave written informed consent for the study. The effects of ribavirin on chronic hepatitis C infection were assessed from changes in serum aminotransferase activities, HCV RNA titers and liver histopathological appearance. These changes were compared by paired Student's t test for statistical significance.

RESULTS

Thirteen patients were treated (Table 1). They comprised 10 men and 13 women with a mean age 44 yr (range = 32 to 66 yr) and a mean known duration of chronic hepatitis of 8.8 yr (range = 1.2 to 18 yr). The sources of hepatitis was presumed to be intravenous drug abuse in seven patients (54%) and blood transfusion in four patients (31%); source was unknown in two patients (15%). Anti-HCV was detectable in 12 patients (92%) and HCV RNA was found in all 13 patients before treatment. Liver biospy specimens taken before treatment showed CAH in nine patients (69%) and active cirrhosis in four patients (31%).

Serum ALT activities decreased progressively during therapy in all patients (Fig. 1). The decrease in ALT was gradual; by 2 mo, the mean percentage decrease in ALT values was 37%; after 4 mo it was 61% and by the end of therapy (6 mo) it was 67% (Table 2). Serum ALT values became normal during therapy in four patients (31%) after 8 wk in two patients, after 12 wk in 1 patient and after 24 wk in another patient. Serum AST activities followed a similar pattern.

The dose of ribavirin was increased to 1,200 mg/day after 4 mo of treatment in seven patients. In one case the dose was not increased, despite a serum ALT of 75 U/L at 4 mo, because of concerns about anemia in the patient. All 13 patients were followed for at least 12 mo after stopping ribavirin therapy. Serum aminotransferase activities rose in all but one patient after discontinuation of therapy, usually approaching pretreatment levels within 2 to 3 mo (Fig. 1). The course of a typical respone is shown in Figure 2. One patient appeared to have a long-term response, with normal serum aminotransferase activities persisting for at least 15 mo after the drug was stopped.

HCV RNA remained detectable in serum in all patients throughout the trial and follow-up. The geometric mean titer of HCV RNA decreased from 1:2,424 to 1:203 after 6 mo of therapy ($p < 0.02$) (Table 3, Fig. 3). Interestingly, although the serum aminotransferase levels had risen in most cases within 3 mo of cessation of ribavirin therapy, levels of HCV RNA did not rise immediately after cessation of therapy and in some cases fell further. However, mean HCV RNA levels had risen to pretreatment levels by 6 mo after cessation of ribavirin therapy.

Comparison of pretreatment and posttreatment liver biopsy samples showed that neither the mean histologicl activity index nor the current hepatic injury ranking decreased with therapy. The mean histological activity

index was 12.9 before and 13.8 after treatment,

[CHART]

Fig. 2. Serial changes in serum ALT activity and HCV RNA titer in a patient with chronic hepatitis C infection treated with ribavirin. The aminotransferase values became normal after 8 wk; levels of HCV RNA in serum decreased, but the viral gonome was still detectable throughout therapy.

TABLE 1. PRETREATMENT SEROLOGICAL AND SERUM BIOCHEMICAL CHARACTERISTICS OF 13 PATIENTS WITH CHRONIC HEPATITIS C INFECTION TREATED WITH RIBAVIRIN

<TABLE>
<CAPTION>

FEATURE	MEAN VALUE	NO.	RANGE	PERCENTAGE
<S>	<C>	<C>	<C>	<C>
Serum ALT (U/L)	210	--	109-593	--
Serum AST (U/L)	132	--	66-261	--
Serum bilirubin (mg/dl)	1.0	--	0.4-2.4	--
Prothrombin time (sec)	12.4	--	11.6-14.6	--
Anti-HCV positive	--	12	--	92
HCV RNA positive	--	13	--	100
Anti-HBc positive	--	5	--	38

</TABLE>
Anti-HBc = antibody to HBcAg.

and the mean current hepatic injury rankings were 13.9 vs. 13.1, respectively.

The most prominent side effect of therapy was mild hemolytic anemia (Fig. 4). The mean hematocrit level decreased from 42.8% to 38.2% (mean decrease = 11%; p less than 0.00007). The mean reticulocyte count rose from 2.1% to 5.6% (p less than 0.0007), and bilirubin values rose from 0.92 mg/dl to 1.43 mg/dl (p less than 0.009). No patient experienced symptomatic anemia. Serum haptoglobin levels fell in all but three patients and became undetectable in six. The only patient who had no evidence of hemolysis during ribavirin therapy had had a splenectomy.

One patient with a previous history of gout experienced acute podagra associated with hyperuricemia during the third month of therapy. However, the overall mean uric acid levels in the 13 patients did not change significantly during ribavirin therapy (5.9 mg/dl before therapy vs. 6.3 mg/dl at the end of therapy).

DISCUSSION

Interferon-alpha has been shown to be effective and is now licensed for use in treatment of chronic hepatitis C in the United States. In approximately 50% of cases, interferon therapy is associated with a rapid decrease in serum aminotransferases to normal, an improvement in liver histopathological appearance and the disappearance of HCV RNA in serum (6, 7, 13). However, patients with hepatitis C often relapse after stopping interferon, and interferon treatment may be associated with clinically significant side effects.

[CHART]

Fig. 3. Serial changes in mean titers of HCV RNA during and after therapy with ribavirin. Levels decreased significantly by the end of therapy and remained suppressed for at least 3 mo after therapy.

Ribavirin is a nucleoside analog agent with a broad spectrum of antiviral activity. Although its mechanism of action remains uncertain, it appears to inhibit the replication of RNA viruses in cell culture by inhibiting viral RNA-dependent RNA polymerase, by depleting intracellular guanine pools and by interfering with the "capping" of viral RNAs (9). Ribavirin therapy is of proven benefit against several RNA viruses that infect human beings, including respitatory syncytial virus infections in children and certain viral hemorrhagic fevers (14, 15). In a preliminary study, Reichard and coworkers found that ribavirin, when administered for 12 wk to patients with chronic hepatitis C, was associated with a significant decline in serum aminotrans-

TABLE 2. CHANGES IN SERUM ALT ACTIVITIES AFTER RIBAVIRIN THERAPY FOR 6 MO IN 13 PATIENTS WITH CHRONIC HEPATITIS C INFECTION

<TABLE>
<CAPTION>

	ALT (U/L)				
PATIENT NO.	BEFORE TREATMENT	AFTER 3 MO OF TREATMENT	AFTER 6 MO OF TREATMENT	3 MO AFTER TREATMENT	6 MO AFTER TREATMENT
<S>	<C>	<C>	<C>	<C>	<C>
1	208	95	71	256	121
2	252	121	74	102	189
3	171	45	69	438	131
4	177	37	22	39	49
5	593	136	99	277	303
6	82	45	36	39	60
7	151	54	54	200	179
8	181	123	79	134	114
9	153	76	24	136	49
10	124	37	41	63	85
11	115	61	58	148	96
12	214	121	108	295	190
13	305	139	86	325	316
Mean	210	84(a)	63(b)	188	145(c)

</TABLE>

(a) p less than 0.005.
(b) p less than 0.0005.
(c) p less than 0.01.

TABLE 3. CHANGES IN SERUM HCV RNA LEVELS AFTER RIBAVIRIN THERAPY IN 18 PATIENTS WITH CHRONIC HEPATITIS C INFECTION

<TABLE>
<CAPTION>

	HCV RNA (RECIPROCAL TITER)				
PATIENT NO.	BEFORE TREATMENT	AFTER 3 MO OF TREATMENT	AFTER 6 MO OF TREATMENT	3 MO AFTER TREATMENT	6 MO AFTER TREATMENT

<S>	<C>	<C>	<C>	<C>	<C>
1	10,000	1,000	1,000	100	100
2	1,000	100	10	10	1,000
3	100	100	1,000	100	10,000
4	10,000	10,000	10	100	10,000
5	1,000	10,000	1,000	10,000	1,000
6	10,000	10,000	10,000	100	10,000
7	1,000	1,000	1,000	1,000	100,000
8	1,000	1,000	1,000	1,000	1,000
9	1,000	1,000	100	100	1,000
10	10,000	100	10	100	1,000
11	1,000	10,000	10	10	1,000
12	10,000	1,000	100	100	10,000
13	10,000	1,000	1,000	1,000	10,000
GMT	2,424	1,194	203	170	2,894

</TABLE>

GMT = geometric mean titer. The HCV RNA end-point dilution titer is determined by detecting HCV RNA in serial dilutions of RNA from 6.25 micron l serum.

ferase activities (16). We therefore tested the effect of ribavirin for a longer period (24 wk) and evaluated changes in HCV RNA and liver histopathological appearance and serum aminotransferases.

In this pilot study, ribavirin therapy was associated with a significant decrease in serum aminotransferases and levels of HCV RNA. In contrast to the type of response seen with interferon, the decrease in aminotransferase activities associated with ribavirin was more gradual. Thus, with interferon, the maximal decrease in mean ALT values (70%) was noted after 1 mo of therapy, wherease with ribavirin the maximal decrease (67%) occurred after a full 6 mo of therapy. Interestingly, serum ALT activities decreased by at least 50% in all treated patients, wherease up to 50% of patients treated with interferon had no decreases in serum aminotransferases at all (6, 7, 13). Although the mean titer of HCV RNA among all patients fell during therapy, RNA levels did not decrease at all in five patients even though their serum aminotransferase levels were lower after therapy.

No improvement was noted in the histological severity of the hepatitis after 6 mo of therapy. This may have been related to the relatively slow decline in serum aminotransferase levels and the fact that the HCV genome did not disappear from serum. Alternatively, the improvement in ALT documented in this study may not truly reflect improvement in the underlying liver disease. Perhaps longer courses of therapy with biopsy specimens taken after several months of maximal

decrease of serum aminotransferases will reveal a beneficial effect of ribavirin in chronic hepatitis C infection.

(CHART)

Fig. 4. Mean percentage changes in hematocrit values, reticulocyte counts and total serum bilirubin concentrations during ribavirin therapy in 13 patients with chronic hepatitis C infection.

The fact that the serum aminotransferase levels began to rise again after cessation of ribavirin therapy confirms that HCV infection was not completely eliminated. However, HCV RNA levels may have remained suppressed for several months after ribavirin therapy ended because of the relatively long half-life of ribavirin in serum (approximately 29 hr)(17).

The hemolysis associated with ribavirin was reversible and not

clinically significant in any patient. The mechanism by which ribavirin causes hemolysis remains uncertain but may be related to its accumulation in RBCs. The observation that ribavirin was well tolerated suggests that ribavirin can be given for prolonged periods. Ribavirin has been reported to be teratogenic in rats, with decreased postnatal survival in pups born to rats treated with very high doses of ribavirin (90 mg/kg/day). No significant teratogenic effects were noted in rabbits or baboons treated similarly (18). No reports have been made of teratogenicity in human subjects treated with ribavirin during pregnancy (Fernandez H. Viratek, Inc., Personal communication, 1991). However, the use of ribavirin should be avoided in pregnancy.

In concthe results of this pilot study of ribavirin therapy in chronic hepatitis C infection suggest that ribavirin has significant antiviral activity against HCV. Ribavirin therapy was very well tolerated, and no patient had clinically significant side effects. The role of long-term therapy (>6 mo) in inducing prolonged remission of hepatitis C with histological improvement should be explored further.

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