

Notice: Because of its potential clinical implications, this article is being published early (on October 1, 2001). It will appear in the November 15 issue of the *Journal*.

TREATMENT OF ACUTE HEPATITIS C WITH INTERFERON ALFA-2b

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ABSTRACT

Background In people who are infected with the hepatitis C virus (HCV) chronic infection often develops and is difficult to eradicate. We sought to determine whether treatment during the acute phase could prevent the development of chronic infection.

Methods Between 1998 and 2001, we identified 44 patients throughout Germany who had acute hepatitis C. Patients received 5 million U of interferon alfa-2b subcutaneously daily for 4 weeks and then three times per week for another 20 weeks. Serum HCV RNA levels were measured before and during therapy and 24 weeks after the end of therapy.

Results The mean age of the 44 patients was 36 years; 25 were women. Nine became infected with HCV through intravenous drug use, 14 through a needle-stick injury, 7 through medical procedures, and 10 through sexual contact; the mode of infection could not be determined in 4. The average time from infection to the first signs or symptoms of hepatitis was 54 days, and the average time from infection until the start of therapy was 89 days. At the end of both therapy and follow-up, 42 of the 43 patients who have completed follow-up (98 percent) had undetectable levels of HCV RNA in serum and normal serum alanine aminotransferase levels. Levels of HCV RNA became undetectable after an average of 3.2 weeks of treatment. Therapy was well tolerated in all but one patient, who stopped therapy after 12 weeks because of side effects.

Conclusions Treatment of acute hepatitis C with interferon alfa-2b prevents chronic infection.

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CHRONIC infection with hepatitis C virus (HCV) is the leading cause of chronic liver disease in the United States and the most common indication for liver transplantation.^{1,2} Almost 4 million people in the United States and about 170 million people worldwide are estimated to be infected,^{3,4} and cirrhosis will eventually develop in 10 to 30 percent of these people.^{4,5} Since the introduction of programs that screen blood products for HCV, less than 10 percent of new infections are caused by transfusions of contaminated blood. New infections continue to occur through such routes as intravenous drug abuse and sexual transmission.³ Progression from acute to chronic HCV infection occurs in 50 to 84 percent of cases⁶⁻¹¹; however, current therapies for chronic infection are not very effective. Even the latest approach — combination therapy with peginterferon alfa-2a or 2b and ribavirin — elim-

inates the virus in only 54 to 56 percent of cases of chronic infection.^{12,13} An alternative approach is to treat the acute infection early with the goal of preventing progression.

Two pieces of evidence suggest that early treatment can prevent the progression of chronic infection. First, in patients with acute human immunodeficiency virus (HIV) infection, antiretroviral therapy sufficiently decreased the viral load to allow the patients' immune systems subsequently to control viral replication.^{14,15} Second, early control of viral load in a murine model of lymphocytic choriomeningitis virus infection enabled the host's immune system to clear the virus and thus prevent the development of chronic infection.¹⁶⁻¹⁸ In contrast, if viral replication is not controlled early, virus-specific CD4 T cells and CD8 T cells are deleted from the T-cell repertoire by apoptosis or are rendered anergic. The strong responses of CD4 T cells^{19,20} and CD8 T cells²¹⁻²⁴ to acute HCV infection in humans are similar to those in the murine model of lymphocytic choriomeningitis virus infection. These strong immune responses during acute infection are weakened if viral replication is not controlled.²⁵

In the light of these data, we assessed whether early control of viral replication in patients with acute HCV infection could prevent the development of chronic hepatitis. Since the viral load in such patients again begins to rise 24 hours after the administration of a single dose of interferon alfa-2b,²⁶ we decided to use a daily dosing regimen for the first four weeks of therapy rather than the standard of three times a week. Treatment was then continued for another 20 weeks according to the standard schedule. Most patients with acute HCV infection are commonly seen first by physicians in private practice. In order to enroll such patients, we conducted a nationwide, prospective study in Germany with the support of the German Association for the Study of the Liver.

METHODS

Selection of Patients

Adult patients (18 to 65 years of age) were eligible if they had an acute HCV infection, were positive for HCV RNA according

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to a polymerase-chain-reaction (PCR) assay, and had elevated serum alanine aminotransferase levels. Acute HCV infection was considered to be present if at least one of the following criteria was met: known or suspected exposure to HCV within the preceding four months, documented seroconversion to positivity for antibodies against HCV, or a serum alanine aminotransferase level of more than 350 U per liter (20 times the upper limit of the normal range), with a documented normal level during the year before the infection (normal range, 0 to 17 U per liter for women and 0 to 22 U per liter for men). The high cutoff value for alanine aminotransferase was chosen to prevent the inclusion of patients with chronic hepatitis among patients who did not fulfill the first or second criterion. In the case of patients who had elevated serum alanine aminotransferase levels and positive tests for HCV RNA, but who had no clear exposure to the virus, toxic hepatitis or superinfection with other hepatitis viruses was ruled out. Patients were excluded if they had decompensated liver disease, liver diseases unrelated to HCV infection, anemia (defined by a hemoglobin level of less than 12 g per deciliter in women and of less than 13 g per deciliter in men), leukopenia (defined as a leukocyte count of less than 3000 per cubic millimeter), thrombocytopenia (defined as a platelet count of less than 100,000 per cubic millimeter), decompensated renal disease (defined by a serum creatinine level of more than 1.5 mg per deciliter [130 μ mol per liter]), decompensated thyroid disease, infection with HIV or hepatitis B virus, psychiatric conditions such as severe depression, a history of seizures, poorly controlled autoimmune diseases, a history of organ transplantation, or ongoing abuse of intravenous drugs or alcohol.

Study Design

In order to recruit a sufficient number of patients with acute hepatitis infection, we had more than 7000 brochures about the study distributed to hospitals, outpatient clinics, private practices, patient-advocacy groups, and the Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (the Central Registry of Work-Related Accidents), which receives data on all work-related accidents in Germany, including needle-stick injuries, even if they do not result in the transmission of any diseases. The brochures also contained detailed recommendations for screening for HCV infection after exposure. Employees of Essex-Pharma (Munich, Germany) helped deliver the brochures to hospitals and private practices, and the study was supported in part by an unrestricted research grant from Essex-Pharma. The study was approved by the ethics committee of the University of Hannover, the Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege, and the German Association for the Study of the Liver. All patients provided written informed consent.

The patients received 5 million U of interferon alfa-2b (Intron A, Essex-Pharma) subcutaneously daily for the first 4 weeks, followed by a dose of 5 million U three times a week for another 20 weeks. All patients were evaluated as outpatients before therapy (week 0); at weeks 2, 4, 12, and 24 of therapy; and 24 weeks after the end of therapy.

Biochemical and hematologic testing was performed by the laboratory at each participating center. Serum levels of HCV RNA were determined centrally, at the Hannover Medical School, before treatment and after each visit (weeks 0, 2, 4, 12, 24, and 48) with use of a reverse-transcription-PCR assay (Cobas Amplicor HCV C monitor, version 2.0, Roche Diagnostics, Mannheim, Germany) that has a lower limit of detection of 600 copies of HCV RNA per milliliter. Viral genotypes were also determined centrally with use of a second-generation assay (INNO-LiPA HCV II Kit, Innogenetics, Heiden, Germany).

Assessment of Efficacy

The primary end point was a sustained virologic response, defined by the absence of detectable levels of HCV RNA in serum 24 weeks after the end of treatment. Secondary end points were the absence of detectable levels of HCV RNA in serum at the end of therapy and the normalization of serum alanine aminotransferase levels.

Statistical Analysis

We used Student's t-test for paired samples to calculate P values related to blood tests. The comparison was with values before the start of therapy. A P value of less than 0.05 was considered to indicate statistical significance. All P values were two-tailed.

RESULTS

Base-Line Characteristics of the Patients

Forty-four patients fulfilled the inclusion criteria and were treated at a total of 24 centers from March 1998 until March 2001 (1 center treated 15 patients, another center 4 patients, 3 centers treated 2 patients each, and the remaining centers treated a single patient each). All 44 patients were treated, and 43 completed therapy according to the protocol; the remaining patient stopped therapy after 12 weeks because of hair loss and influenza-like symptoms. Forty-three patients have completed follow-up. Thirty patients (68 percent) met the first criterion of known or suspected exposure to HCV during the preceding four months (Table 1); 17 of these patients also had documented seroconversion. An additional six patients had documented seroconversion but did not have a documented exposure (three of whom had HCV-positive partners and three for whom the mode of transmission was unclear). Eight patients met only the third criterion, since they had serum alanine aminotransferase levels ranging from 635 to 1500 U per liter with no prior signs of liver disease (six of whom had HCV-positive partners and two for whom the mode of transmission was unclear).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 44 PATIENTS.*

CHARACTERISTIC	VALUE
Age — yr	36 \pm 11
Female sex — no. (%)	25 (57)
Icterus — no. (%)	30 (68)
Mode of infection — no. (%)	
Intravenous drug use	9 (20)
Needle-stick injury	14 (32)
Medical procedure†	7 (16)
Sexual contact with HCV-positive partners	10 (23)
Unclear	4 (9)
Viral load — copies of HCV RNA $\times 10^{-6}$ /ml	0.42 \pm 0.93
Alanine aminotransferase — (U/liter)	885 \pm 554
HCV genotype — no. (%)	
1	27 (61)
2 or 3	12 (27)
4	0
Unclear	5 (11)

*Plus-minus values are means \pm SD.

†The medical procedures consisted of dental surgery, aortic-valve replacement, gynecologic laparoscopy, tonsillectomy, resection of sigmoid colon, skin surgery, and varicose-vein surgery.

All 44 patients had hepatitis as defined by elevated serum alanine aminotransferase levels (lowest level, 140 U per liter) (Table 1). Seroconversion was documented in 52 percent. The most frequent sources of infection were a needle-stick injury (in 32 percent of patients), sexual contact with HCV-positive partners (in 23 percent), intravenous drug use (in 20 percent), and medical procedures (in 16 percent). All seven medical procedures were surgical in nature. The average time from infection to the first signs or symptoms of disease was 54 days (range, 15 to 105), and the average time from infection until the start of therapy was 89 days (range, 30 to 112).

Efficacy

In all 44 patients, serum levels of HCV RNA became undetectable during therapy (Fig. 1). The average time for levels of HCV RNA to become undetectable after the beginning of treatment was 3.2 weeks (range, 2 to 12). After 24 weeks of follow-up, 42 of the 43 patients who have completed follow-up (98 percent) had undetectable levels of HCV RNA.

Serum levels of alanine aminotransferase fell rapidly during therapy and normalized within 10.4 weeks after the initiation of treatment (range, 2 to 48). At the end of the 24 weeks of therapy, 80 percent of the patients had a normal serum alanine aminotransferase level. The remaining 20 percent of patients had only a mild elevation in alanine aminotransferase, with

levels not more than twice the upper limit of the normal range. All 9 of these patients had normal liver-enzyme values after the end of therapy, and the 42 patients who had undetectable levels of HCV RNA after 24 weeks of follow-up also had normal serum alanine aminotransferase levels by the end of follow-up.

One patient, who stopped therapy after 12 weeks, had a self-limited flare of hepatitis with HCV viremia at week 20 and subsequently had undetectable levels of HCV RNA in serum. The patient had persistently normal levels of aminotransferases and had no detectable serum levels of HCV RNA during a further follow-up of 12 months after the relapse of hepatitis. Another patient, who had stable multiple sclerosis, received a short course of pulsed corticosteroids at week 17 for neurologic symptoms while continuing to receive interferon alfa-2b. Although the neurologic symptoms improved, the patient's serum alanine aminotransferase levels increased 15 days after the end of interferon therapy. She had a positive HCV RNA assay 35 days after therapy ended. Because of the persistently elevated alanine aminotransferase levels and the rising levels of HCV RNA, the patient received combination therapy with interferon alfa-2a (6 million U subcutaneously three times a week) and ribavirin (400 mg twice a day) starting 89 days after therapy ended. She had undetectable serum levels of HCV RNA and normal serum levels of alanine aminotransferase after three weeks of combination therapy. These findings

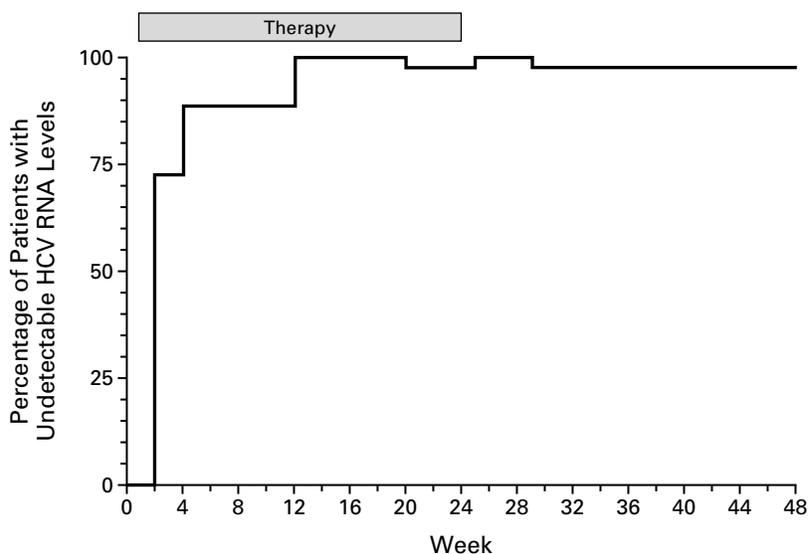


Figure 1. Cumulative Incidence of Undetectable Serum Levels of HCV RNA during Treatment and Follow-up.

All 44 patients were evaluated before therapy (week 0) and at weeks 2, 4, 12, and 24 of therapy, and 43 patients were evaluated 24 weeks after the end of therapy. Serum HCV RNA levels were measured by a reverse-transcription-polymerase-chain-reaction assay for which the lower limit of detection is 600 copies of HCV RNA per milliliter.

were still present at the time of her most recent follow-up (week 37 of combination therapy), and no further neurologic deterioration was noted.

Safety

Therapy was well tolerated in all patients except the one who discontinued treatment. The spectrum of side effects was similar to that reported in previous trials of monotherapy with interferon alfa-2b.^{27,28} There were no serious adverse effects during therapy. The incidence of adverse effects was not higher during the initial 4 weeks of daily dosing than during the subsequent 20 weeks. None of the 43 patients who completed treatment required a dose modification. No signs of decreased liver function (as measured clinically and on the basis of coagulation activity and serum albumin levels) were noted during acute HCV infection, interferon therapy, or the hepatitis flares in the two patients who had relapses. In all patients, thrombocytopenia (mean [\pm SD] platelet count at week 4, $161,000 \pm 43,000$ per cubic millimeter, as compared with $250,000 \pm 66,000$ per cubic millimeter before therapy; $P < 0.001$) and leukopenia (mean leukocyte count at week 4, 3900 ± 1100 per cubic millimeter, as compared with 6600 ± 1500 per cubic millimeter before therapy; $P < 0.01$) developed during therapy and resolved after the end of therapy.

DISCUSSION

We found that early treatment of acute hepatitis C with interferon alfa-2b alone prevented the development of chronic HCV infection in almost all patients. The response to interferon alfa-2b was not influenced by the viral genotype, the patients' sex, or the mode of transmission. The use of interferon alone rather than in combination with ribavirin — the standard therapy for chronic HCV infection — results in fewer side effects and lower costs. Furthermore, a 24-week course of treatment was sufficient to prevent chronic infection. The suggested course of treatment is 48 weeks in patients with chronic infections with HCV genotype 1a or 1b.^{27,28} Even shorter periods of treatment might be sufficient in patients in whom serum levels of HCV RNA quickly become undetectable.

There is no standard therapy for acute HCV infection.²⁹ Several studies have evaluated the efficacy of interferon therapy for acute HCV infection,^{6,8,30-41} and all but one⁸ reported a beneficial effect of treatment. However, these studies had substantial limitations. Some included primarily patients with transfusion-associated HCV infection,³⁰⁻³⁸ some were very small,^{6,33,35,37,39-41} and others used interferon beta^{8,34,35} or treated patients for only a short period.^{8,30-32,34-36,40} Not all studies measured outcome on the basis of serum levels of HCV RNA^{31,36-38} A larger prospective trial with a more representative group of patients was therefore needed.^{3,42}

We enrolled a large number of patients in a short period by conducting a nationwide study that included a suggested protocol for screening after suspected exposure to HCV. Although it is possible that our findings apply only to a subgroup of seriously ill patients, we believe that our methods of enrollment minimized the likelihood of a referral bias.

We did not include a placebo group. However, when our results are compared with those among patients who did not receive therapy after acute HCV infection, the beneficial effect of early treatment is clear. A group of 40 untreated patients who were seen and prospectively followed during a similar observation period (1995 to 2000) at the clinic of infectious diseases of the University of Bari in Italy⁴³ had base-line characteristics (mean age, 40 years; 42 percent were women, and 50 percent had icterus) and a distribution of HCV genotypes (53 percent had genotype 1, 35 percent had genotype 2 or 3, and 5 percent had genotype 4) that were similar to those of our patients. Chronic HCV infection developed in 70 percent of these untreated patients. This rate is similar to the rate of chronic infection in other studies.^{4,44} Although rates of conversion to chronic HCV infection of 50 to 55 percent have been found in some groups of children⁴⁵ and young women,^{7,11} most studies have reported rates of 70 to 84 percent, even after the exclusion of patients with transfusion-associated HCV.^{3,6,8,14,41,44,46}

It is likely that about 30 percent of our patients would have had self-limited disease, regardless of whether they received interferon alfa-2b. So far, there are no means to identify such patients at presentation.⁴² Since the current treatment for chronic HCV infection eliminates the virus in only about half of cases,^{12,13,38} we suggest that all patients with acute hepatitis C should be treated. The value of other treatments, such as peginterferon alfa, should also be studied. Since all our patients had hepatitis, as defined by an elevated serum alanine aminotransferase level, our findings may not apply to patients with HCV RNA in serum and normal serum liver-enzyme levels after acute infection. However, we did not identify any such patients during our national study.

In summary, early treatment of acute hepatitis C with interferon alfa-2b alone (5 million U per day for the first 4 weeks, followed by a dose of 5 million U three times a week for another 20 weeks) prevents the development of chronic HCV infection in most patients.

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APPENDIX

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REFERENCES

- National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. *Hepatology* 1997;26:Suppl 1:2S-10S.
- Detre KM, Belle SH, Lombardero M. Liver transplantation for chronic viral hepatitis. *Viral Hepatitis Rev* 1996;2:219-28.
- Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999;341:556-62.
- Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liver Dis* 2000;20:17-35.
- Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997;349:825-32.
- Delwaide J, Bourgeois N, Gerard C, Wain E, Vaira D, Belaiche J. Treatment of acute hepatitis C with interferon α -2b prevents chronicity. *Hepatology* 1999;30:Suppl:264A. abstract.
- Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. *N Engl J Med* 1999;340:1228-33.
- Calleri G, Colombatto P, Gozzelino M, et al. Natural beta interferon in acute type-C hepatitis patients: a randomized controlled trial. *Ital J Gastroenterol Hepatol* 1998;30:181-4.
- Parana R, Vitvitski L, Andrade Z, et al. Acute sporadic non-A, non-B hepatitis in northeastern Brazil: etiology and natural history. *Hepatology* 1999;30:289-93.
- Pape GR, Gerlach TJ, Diepolder HM, Gruner N, Jung M, Santantonio T. Role of the specific T-cell response for clearance and control of hepatitis C virus. *J Viral Hepat* 1999;6:Suppl 1:36-40.
- Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in Germany: a 20-year multicenter study. *Hepatology* 2000;32:91-6.
- Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b in combination with ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: results of a randomized trial. *Lancet* 2001;358:958-65.
- Fried MW, Shiffman ML, Reddy RK, et al. Pegylated (40 kDa) interferon alfa-2a (PEGASYS) in combination with ribavirin: efficacy and safety results from a phase III, randomized, actively-controlled, multicenter study. *Gastroenterology* 2001;120:Suppl:A-55. abstract.
- Rosenberg ES, Altfeld M, Poon SH, et al. Immune control of HIV-1 after early treatment of acute infection. *Nature* 2000;407:523-6.
- Rosenberg ES, Billingsley JM, Caliendo AM, et al. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. *Science* 1997;278:1447-50.
- Zinkernagel RM. Immunology taught by viruses. *Science* 1996;271:173-8.
- Moskophidis D, Lechner F, Pircher H, Zinkernagel RM. Virus persistence in acutely infected immunocompetent mice by exhaustion of antiviral cytotoxic effector T cells. *Nature* 1993;362:758-61. [Erratum, *Nature* 1993;364:262.]
- Oxenius A, Zinkernagel RM, Hengartner H. Comparison of activation versus induction of unresponsiveness of virus-specific CD4+ and CD8+ T cells upon acute versus persistent viral infection. *Immunity* 1998;9:449-57.
- Gerlach JT, Diepolder HM, Jung M-C, et al. Recurrence of hepatitis C virus after loss of virus-specific CD4(+) T-cell response in acute hepatitis C. *Gastroenterology* 1999;117:933-41.
- Missale G, Bertoni R, Lamonaca V, et al. Different clinical behaviors of acute hepatitis C virus infection are associated with different vigor of the anti-viral cell-mediated immune response. *J Clin Invest* 1996;98:706-14.
- Takaki A, Wiese M, Maertens G, et al. Cellular immune responses persist and humoral responses decrease two decades after recovery from a single-source outbreak of hepatitis C. *Nat Med* 2000;6:578-82.
- Gruener NH, Gerlach TJ, Jung M-C, et al. Association of hepatitis C virus-specific CD8+ T cells with viral clearance in acute hepatitis C. *J Infect Dis* 2000;181:1528-36.
- Lechner F, Gruener NH, Urbani S, et al. CD8+ T lymphocyte responses are induced during acute hepatitis C virus infection but are not sustained. *Eur J Immunol* 2000;30:2479-87.
- Lechner F, Wong DK, Dunbar PR, et al. Analysis of successful immune responses in persons infected with hepatitis C virus. *J Exp Med* 2000;191:1499-512.
- Rehermann B. Interaction between the hepatitis C virus and the immune system. *Semin Liver Dis* 2000;20:127-41.
- Lam NP, Neumann AU, Gretch DR, Wiley TE, Perelson AS, Layden TJ. Dose-dependent acute clearance of hepatitis C genotype 1 virus with interferon alfa. *Hepatology* 1997;26:226-31.
- Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998;352:1426-32.
- McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 1998;339:1485-92.
- European Association for the Study of the Liver. EASL International Consensus Conference on hepatitis C: Paris, 26-28, February 1999, consensus statement. *J Hepatol* 1999;30:956-61.
- Hwang SJ, Lee SD, Chan CY, Lu RH, Lo KJ. A randomized controlled trial of recombinant interferon alpha-2b in the treatment of Chinese patients with acute post-transfusion hepatitis C. *J Hepatol* 1994;21:831-6.
- Viladomiu L, Genesca J, Esteban JI, et al. Interferon-alpha in acute posttransfusion hepatitis C: a randomized, controlled trial. *Hepatology* 1992;15:767-9.
- Lampertico P, Rumi M, Romeo R, et al. A multicenter randomized controlled trial of recombinant interferon- α_{2b} in patients with acute transfusion-associated hepatitis C. *Hepatology* 1994;19:19-22.
- Alberti A, Chemello L, Belussi F, Pontisso P, Tisminetzky S, Gerotto M. Outcome of acute hepatitis C and role of interferon alpha therapy. In: Nishioka KSH, Oda T, eds. *Viral hepatitis and liver disease*. Tokyo, Japan: Springer-Verlag, 1994:604-60.
- Takano S, Satomura Y, Omata M, Japan Acute Hepatitis Cooperative Study Group. Effects of interferon beta on non-A, non-B acute hepatitis: a prospective, randomized, controlled-dose study. *Gastroenterology* 1994;107:805-11.
- Omata M, Yokosuka O, Takano S, et al. Resolution of acute hepatitis C after therapy with natural beta interferon. *Lancet* 1991;338:914-5.
- Ohnishi K, Nomura F, Nakano M. Interferon therapy for acute post-transfusion non-A, non-B hepatitis: response with respect to anti-hepatitis C virus antibody status. *Am J Gastroenterol* 1991;86:1041-9.
- Tassopoulos NC, Koutelou MG, Papatheodoridis G, et al. Recombinant human interferon alfa-2b treatment for acute non-A, non-B hepatitis. *Gut* 1993;34:Suppl:S130-S132.
- Palmovic D, Kurelac I, Crnjakovic-Palmovic J. The treatment of acute post-transfusion hepatitis C with recombinant interferon-alpha. *Infection* 1994;22:222-3.
- Vogel W, Graziadei I, Umlauf F, et al. High-dose interferon-alpha2b treatment prevents chronicity in acute hepatitis C: a pilot study. *Dig Dis Sci* 1996;41:Suppl:81S-85S.
- Lee WM, Shiffman ML, Gnnann JW Jr, Samanta A, Alam J. A trial of interferon beta 1a (IFN β 1a) for 4 weeks for therapy of acute hepatitis C. *Hepatology* 1996;24:Suppl:275A. abstract.
- Pimstone NR, Powell JS, Kotfila R, Pimstone DJ, Davidson L. High dose (780 MIU/52 weeks) interferon monotherapy is highly effective treatment for acute hepatitis C. *Gastroenterology* 2000;118:Suppl:A960. abstract.
- Orland JR, Wright TL, Cooper S. Acute hepatitis C. *Hepatology* 2001;33:321-7.
- Santantonio T, Mazzola M, Guastadisegni A, Casalino C, Pastore G. A cohort study of acute hepatitis C virus (HVC) infection: natural course and outcome. *Hepatology* 1999;30:Suppl:205A. abstract.
- Seef LB. Natural history of hepatitis C. In: Schiff ER, Hoofnagle JH,

eds. Update on viral hepatitis: syllabus of the 2000 AASLD postgraduate course. Alexandria, Va.: American Association for the Study of Liver Diseases, 2000:112-8.

45. Vogt M, Lang T, Frösner G, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the

implementation of blood-donor screening. *N Engl J Med* 1999;341:866-70.

46. Locasciulli A, Testa M, Pontisso P, et al. Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. *Blood* 1997;90:4628-33.

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