Therapy of Acute Hepatitis C

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Acute hepatitis C has a high propensity to become chronic, which provides the rationale for treating patients with acute disease attempting to prevent chronicity. Almost all published studies on therapy of acute hepatitis C have been small in size, uncontrolled, and highly heterogeneous as to patient features, dose and duration of treatment, follow-up evaluation, and criteria used to define efficacy and safety. The published studies on treatment of acute hepatitis C have used standard alfa or beta interferon monotherapy: none have evaluated combination therapy of interferon and ribavirin or peginterferon. Several meta-analyses of published studies have concluded that initiation of interferon monotherapy during the acute phase of hepatitis C virus (HCV) infection significantly reduces (by 30% to 40%) evolution to chronic hepatitis. The tolerability of interferon in acute hepatitis C has been excellent, even in symptomatic and icteric patients; the side effects and adverse events being similar in type and frequency to those seen when treating chronic cases. Thus, currently available data support treatment of patients with acute hepatitis C, but data are insufficient to draw firm conclusions about which patients to treat, when therapy should be started, or what regimen is optimal. Future studies of adequate size and design should focus on efficacy and tolerability of peginterferons and whether therapy should be started immediately after diagnosis or delayed for 2 to 4 months to avoid treatment of patients who spontaneously recover. (HEPATOLOGY **2002;36:S195-S200.**)

Infection with the hepatitis C virus (HCV) is the major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma in many parts of the world. Acute HCV infection is typically mild and often asymptomatic, but has a high propensity to become chronic. The high chronicity rate of acute hepatitis C provides a strong rationale for antiviral therapy during the acute course of the illness, attempting to prevent chronic evolution. This approach has been supported by results of many studies of antiviral therapy in acute hepatitis C, but all have focused on monotherapy with either alfa or beta interferon. Furthermore, these studies have had several shortcomings: most were small in size and were highly heterogeneous as to the types of patients treated, regimen of therapy, and definitions of beneficial responses. There have been no recent studies using more rigorous regimens of therapy, such as combination therapy using interferon and ribavirin or therapy with pegylated forms of interferon (peginterferon). The problems with published studies on therapy of acute hepatitis C are explained by the nature of acute hepatitis C itself. Acute hepatitis C is now relatively uncommon and patients typically present at different stages of the disease with greatly variable signs, symptoms, and biochemical abnormalities. Acute hepatitis C may not be diagnosed correctly and accurate diagnosis may be delayed. The problems in collecting a large number of cases of acute hepatitis C to enroll into a clinical study are many: (1) the epidemiology of the disease has changed during the past decade and the incidence of new infections has decreased in all developed countries, with a dramatic reduction of transfusion-associated forms[1,2]; (2) acute hepatitis C is often clinically mild or completely asymptomatic and rarely is recognized outside prospective surveillance after exposure to known risk factors[3]; (3) there are still no specific diagnostic tests to identify acute infection with HCV and to distinguish it from an acute exacerbation of chronic hepatitis C, and (D) the outcome of acute hepatitis C is variable and not readily predictable from clinical or serologic tests. Although the rate of chronic outcome is high, it can vary from as low as 40% to 50% to as high as 90% to 100% depending on patient age and sex (younger and female patients having a lower rate of chronicity),[4,5] the source of infection and size of inoculum (the highest risk for chronicity appears to

Abbreviations: HCV, hepatitis C virus; ALT, alanine aminotransferase.

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Table 1. Interferon for Acute Hepatitis C. Summary of Published Studies Including 14 Articles and 3 Abstracts

Type of Studies (References)	Number of Studies	Number of Treated Cases (Range)	Number of Untreated Cases (Range)
Randomized controlled trials (treatment vs. untreated)[6-11]	6	105 (11-27)	101 (13-21)
Randomized controlled trials (dose comparison)[12-13]	2	79 (6-17)	–
Controlled, but not randomized trials[14-18]	5	86 (11-36)	100 (10-46)
Uncontrolled trials[19-22]	4	99 (7-44)	–
Total	17	369 (6-44)	201 (10-46)

be associated with posttransfusion hepatitis), and clinical features during the acute phase (asymptomatic cases being more prone to progress to chronic hepatitis compared with cases with symptomatic disease and jaundice). As a consequence of these factors, acute hepatitis C is difficult to study and the amount of information about its natural history and optimal management strategies remains limited.

Published Studies on Interferon Therapy for Acute Hepatitis C

Seventeen studies on therapy of acute hepatitis C have been published either as full articles or in abstract form (Table 1). The 17 studies enrolled a total of 369 treated and 201 untreated patients. Eight studies were prospective, randomized controlled trials comparing treatment with interferon with no treatment[6-11] or different schedules of interferon.[12,13] Five studies were controlled but not randomized,[14-18] and 4 studies lacked a control group and included treated patients only.[19-22] Most studies were small in size and were heterogeneous with respect to: (1) inclusion criteria and patient characteristics; (2) type of interferon used; (3) dose of interferon, schedule of administration, and duration of treatment; (4) criteria used to assess efficacy and safety; and (5) posttreatment follow-up evaluation (Table 2).

Table 2. Heterogeneity of Published Studies on Interferon Therapy of Acute Hepatitis C

Studies	
Posttransfusion cases only	7 studies
Non-posttransfusion cases only	5 studies
Mixed population of cases	5 studies
Patients included	
Symptomatic patients only	7 studies
Symptomatic and asymptomatic patients	10 studies
Percent of patients with jaundice	25% to 100%
Mean pretreatment ALT levels	80 to 1,400 IU/L
Type of interferon used	
Alfa interferon	12 studies
Beta interferon	5 studies
Dose and duration of therapy	
Initial dose	0.3-10 MU
Cumulative dose	8.4-780 MU
Daily	4 studies
3 times weekly	9 studies
Daily and then 3 times weekly	4 studies
Duration of therapy	4-52 wk
Criteria for assessing response	
Biochemical response only	5 studies
Biochemical and virological response	12 studies

Pooling data from the 17 studies, end-of-treatment biochemical responses occurred in 76% (range, 15% to 100%) of treated patients compared with 24% (10% to 44%) of untreated patients, and sustained biochemical responses occurred in 61% (25% to 100%) of treated but only 26% (16% to 50%) of untreated patients (Fig. 1). Importantly, virological responses were recorded in 82% (37% to 100%) of treated compared with 10% (0% to 20%) of untreated patients at the end of treatment, and sustained loss of HCV RNA was found in 62% (37% to 100%) of interferon-treated patients compared with only 12% (0% to 20%) of untreated subjects. Despite the multiplicity, small size, and heterogeneity of these 17 studies, the pooled results strongly support the benefit of interferon therapy in reducing chronicity of acute hepatitis C. This conclusion has been confirmed by using the more rigorous criteria of formal meta-analysis.

Meta-Analysis of Randomized Controlled Trials

Among 6 published, randomized controlled trials in which treated patients were compared with an untreated

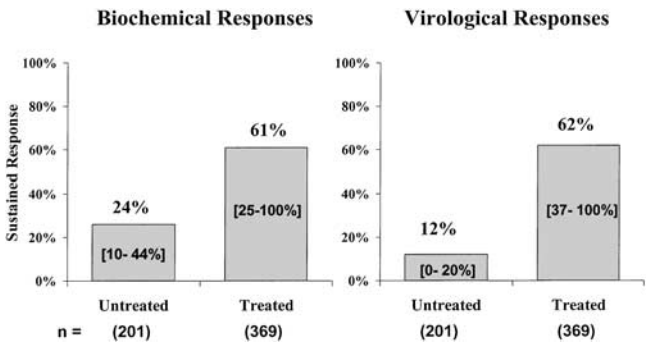

Fig. 1. Combined results from 17 published studies on therapy of acute hepatitis C that included outcomes on a total of 201 untreated and 369 treated patients. Left panel shows overall and range (in brackets) of sustained biochemical responses in untreated and treated patients. Right panel shows overall and range of sustained virological responses in untreated and treated patients.

Table 3. Meta-analysis of 4 Randomized Controlled Trials of Interferon alfa-2b for Acute Posttransfusion Hepatitis C

	Interferon Treated % (95% Confidence Interval)	*P* Value	Untreated % (95% Confidence Interval)	% Increase With Interferon
Biochemical end-of-treatment response	74% (63-84)	.00001	30% (19-42)	45% (31-59)
Virological end-of-treatment response	42% (30-56)	.00001	4% (0-13)	40% (27-53)
Biochemical sustained response	54% (42-66)	.0006	25% (15-37)	29% (11-44)
Virological sustained response	32% (21-46)	.00007	4% (0-13)	29% (16-43)

Reprinted from Poynard et al.[23]

control group, 4[6-9] were conducted in patients with posttransfusion hepatitis using a single regimen of therapy: alfa interferon in a dose of 3 MU 3 times weekly for 12 weeks. These 4 studies included 74 treated and 67 untreated patients (mean age, 51 ± 4 y) and were fairly homogeneous, allowing for appropriate pooling of data for formal meta-analysis (Table 3).[23] Interferon therapy was associated with a statistically significant improvement in outcome, with a 29% increase in rate of sustained virological response compared with no treatment.

These results clearly indicate that interferon monotherapy is associated with a significant reduction of chronicity when given to patients with acute hepatitis C, even when using a relatively low dose of interferon for a relatively short period of time. Nevertheless, the overall response rate was somewhat low and almost two thirds of treated patients still developed chronic infection. The low rate of response may have been owing to the type of patients treated (mostly posttransfusion hepatitis cases), but most likely reflected a suboptimal dose and duration of treatment with interferon. These low rate of response were similar to rates of response to treatment of chronic hepatitis C, which argued against treatment during the acute illness and supported delay in treatment until it was clear that chronic infection had developed and therapy for prevention of progression of chronic liver disease was indicated.

Other Recent Studies

Several recent studies have used more aggressive treatment schedules with higher doses of interferon and/or longer periods of administration and have reported higher rates of sustained virological response, rates far higher than achieved in treating chronic hepatitis C. Unfortunately, most of these studies were conducted without a concurrently randomized, untreated control group. Furthermore, patients in these studies tended to be more heterogeneous, having acquired acute hepatitis C not by transfusion and having varying degrees of disease severity and jaundice. In these cases, rates of spontaneous resolution of acute hepatitis C may be significantly higher than in cases of asymptomatic, posttransfusion hepatitis.[24-26]

Three studies used alfa interferon given initially in doses of 5 to 10 MU daily (Fig. 2). Vogel et al.[19] treated 24 patients with acute symptomatic hepatitis C with alfa interferon in a dose of 10 MU daily until serum alanine aminotransferase (ALT) levels became normal, which occurred within 18 to 43 days of starting therapy. The sustained virological response rate was 83%. Pimstone et al.[20] treated 7 patients with alfa interferon in a dose of 5 MU daily for 12 weeks followed by 3 MU 3 times weekly for an additional 40 weeks. In their study, all 7 patients had a sustained virological response with follow-up of at least 6 months after stopping therapy. More recently, Jaeckel et al.[21] treated 44 patients (mostly with acute, symptomatic hepatitis C) with alfa interferon in a dose of 5 MU daily for 4 weeks followed by 3 times weekly for an additional 20 weeks. In this German, multicenter study, all but one patient (98%) had a sustained response with normal ALT levels and no detectable HCV RNA 6 months after cessation of therapy. Although none of these 3 studies included an untreated control group, the rates of resolution (83% to 100%) were considerably higher than what would be expected to occur spontaneously (30% to 50%) in a matched epidemiologic and clinical setting. On the other hand, single determinations of serum ALT and HCV-RNA levels 6 months after cessation of therapy may not have been adequate to reliably document recovery from hepatitis C because transient phases of viral clear-

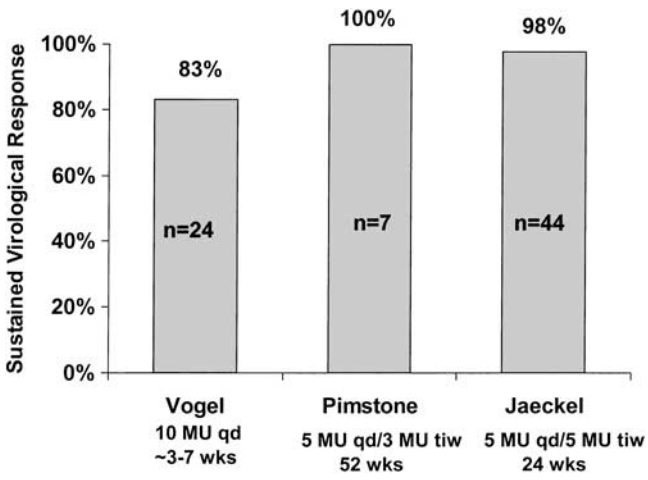

Fig. 2. Sustained virological response rates in 3 recent uncontrolled studies of therapy of acute hepatitis C initially using high daily doses of interferon alfa.[19-21] The number of treated patients is shown.

ance and disease remission can occur during and after the acute phase of hepatitis C even in untreated patients who ultimately develop chronic infection.[22,26] Despite these limitations, these studies suggest that treatment with higher and/or daily doses of alfa interferon may be needed to reliably lead to clearance of virus in acute hepatitis C. The role of a higher interferon dose also was supported by studies of beta interferon from Japan that reported a clear dose-dependent rate of response in treating acute hepatitis C.[12]

In other studies, conducted in similar patient cohorts treated with lower doses of interferon (3-6 MU 3 times weekly for 3-6 mo), rates of sustained virological response ranged from 37% and 64%.[14-18] In those studies in which an untreated control (although not randomized) group was included for comparison, rates of spontaneous resolution were usually lower (8% to 21%), although a statistically significant difference was rarely obtained because of the small number of patients included. Cammà and Craxì[27] have included most of these studies in a recent meta-analysis that concluded that interferon therapy compared with no treatment significantly increased both the biochemical sustained response rates (odds ratio, 4.85; 95% confidence interval, 2.28-10.32) and the virological sustained response rates (odds ratio, 13.54; 95% confidence interval, 7.29-25.16). Findings were similar when randomized and nonrandomized trials were analyzed separately.

Immediate Versus Delayed Treatment

Recent data indicate that the proportion of patients with acute hepatitis C who recover spontaneously might be higher than previously believed and might exceed 50% in young patients with acute icteric and symptomatic disease.[22,26] Unfortunately, there are no reliable markers to predict the outcome early during the course of acute hepatitis C. The most rational strategy to avoid unnecessary treatment of these cases would be to delay therapy and thus offer it only to patients with the highest risk for chronicity, such as those who remain HCV-RNA positive and with elevated ALT levels more than 2 to 4 months after onset.[28,29] Few studies have evaluated whether delaying treatment in acute hepatitis C allows recognition of patients who recover spontaneously and whether this delay results in a decrease in the sustained virological response rate that can be achieved. Actually, in most studies of therapy of acute hepatitis C, treatment was delayed for 1 to 4 months after onset, a period of time needed to recognize the disease and make a positive diagnosis. Thus, available data suggests that delaying therapy by 2 to 4 months after onset may be a reasonable strategy to achieve these goals, but these conclusions are based on limited[14,15] and preliminary experience.[22]

Predictors of Response

In chronic hepatitis C, variables that correlate with a higher likelihood of a sustained response include pretreatment HCV-RNA levels, HCV genotype, female sex, younger age, less hepatic fibrosis on liver biopsy examination, and lower body weight. Because studies of treatment of acute hepatitis have been limited in size and included a heterogeneous population of patients, there have been few analyses of factors that predict a response. Pretreatment HCV-RNA levels were reported in 5 studies, and a statistically significant association between lower initial levels of virus and sustained virological response was found in 3. Interestingly, this association was not evident in studies that used higher doses of interferon (5-10 MU daily). HCV genotypes were reported in 6 studies, but in only 2 was there a significant association between the genotype and response (higher rates with genotypes 2 and 3 than with genotype 1). Factors of age, sex, race, obesity, and liver histology have not been analyzed. However, if response rates are truly as high as 83% to 100% in acute hepatitis C, these factors are unlikely to show a significant correlation with response or lack of response.

Tolerability Profile

A detailed description of side effects of interferon therapy was reported in 9 studies, which included a total of 177 patients, including 70 with jaundice. The tolerability profile of interferon therapy was similar to that usually observed in chronic hepatitis C. Therapy was well tolerated in patients with jaundice and markedly elevated ALT levels. No worsening of ALT levels or deterioration of liver function were observed with initiation of interferon therapy. A single patient was described who received interferon in a dose of 10 MU daily and developed acute lobular hepatitis after clearance of HCV RNA, which required treatment with a short course of corticosteroids.[17] Overall, available data have not indicated higher rates of interferon-associated side effects or unexpected adverse effects in patients with acute hepatitis C when compared with what has been reported in patients treated for chronic hepatitis C.

Conclusions and Unresolved Issues

There is convincing evidence from published studies that interferon monotherapy reduces the rate of progression of acute to chronic hepatitis C. The degree of reduction appears to correlate with patient characteristics and dose and duration of interferon therapy. Published meta-analyses on low-dose interferon monotherapy for 12 weeks indicate that the reduction in chronicity ranges from 30% to 40%. Despite the evidence, however, it is

difficult to make firm recommendations for treatment of acute hepatitis C.[29] Several issues of therapy are unresolved and not fully addressed in the published literature.

Who Should Be Treated? Patients with acute HCV infection are quite heterogeneous. Some individuals being completely asymptomatic and having normal or minimally elevated serum ALT levels despite HCV-RNA positivity after known exposure or needle-stick injury. Other patients present with acute illness and have high serum ALT levels and marked jaundice. Available data suggests that the effects of interferon are independent of clinical features, but more data is needed to better define outcomes with and without therapy in different patient subgroups and to determine safety of therapy in severely ill cases. Indeed, treating patients before onset of symptoms and marked ALT elevations may be counterproductive because the antiviral therapy may only be effective in the setting of an active host immune response to the infection.

When Should Therapy Be Started? Immediate treatment of all cases with acute HCV infection would result in treatment of some patients who would recover spontaneously. Because of the side effects, duration, and expense of therapy, efforts should be made to avoid treating patients unnecessarily. A strategy of delaying therapy by 2 to 4 months after diagnosis would allow giving treatment only to patients with the highest risk for chronicity. This approach is particularly appropriate in categories of patients in whom a high rate of spontaneous recovery is expected, such as children, young adults (particularly women), and patients with jaundice. What is unclear is whether delaying therapy reduces the efficacy of interferon treatment, perhaps owing to expansion of HCV quasispecies toward a more heterogeneous and resistant virus population or to blunting of the immune response, features that appear to correlate with evolution into chronicity. Available data, albeit limited, suggests that delaying therapy by 2 to 4 months does not compromise the probability of a favorable response to interferon.

What Regimen of Therapy Should Be Used? The optimal regimen of therapy in acute hepatitis C has not been defined, particularly in terms of risk versus benefit and cost versus effectiveness. There have been no studies of interferon-ribavirin combination therapy nor of the newly developed peginterferons. In chronic hepatitis C, these regimens are considerably more effective than standard interferon monotherapy. Yet regimens of high doses of daily interferon monotherapy appear to be highly effective in acute hepatitis C. Available data indicate that the minimum requirement for obtaining a significant benefit (in comparison with no treatment) is 3 MU of alfa interferon given 3 times weekly for at least 12 weeks. However, this regimen was associated with a sustained virological response of only 30% to 40%. More aggressive regimens, based on induction with daily interferon (5-10 MU) followed by 3 times weekly therapy for 4 to 6 months, may allow the achievement of a sustained virological response (defined at 24 weeks after cessation of therapy) in almost 100% of cases. How this dose of standard interferon may compare with doses of peginterferon is unknown.

What Long-Term Follow-Up Evaluation Is Needed After Treatment? Studies on the natural history of acute hepatitis C have indicated the need for an accurate and prolonged virological follow-up evaluation to predict long-term outcomes. In many patients with acute hepatitis C there is a transient phase of HCV-RNA negativity during recovery from the acute illness despite the eventual evolution to chronicity. Most published studies of interferon treatment of acute hepatitis C have included too few follow-up samples to completely document the resolution of infection. For the present, long-term follow-up evaluation at least 48 weeks after therapy seems appropriate to ensure that the HCV infection has resolved.

Future Research Needs

Future research on the treatment of acute hepatitis C should be conducted through prospective, randomized trials of adequate size and design. Three areas of focus are of greatest priority.

Therapeutic Regimen. Assessment of the efficacy and safety of peginterferon monotherapy in acute hepatitis C using a standard dose and comparing different durations of treatment is needed. A 6-month course of peginterferon seems the most rational approach, but shorter treatment periods would be highly worthwhile. The addition of ribavirin may not be necessary as the first choice for acute hepatitis C, but a possible role of combination therapy with ribavirin deserves prospective analysis as well.

Timing of Therapy. Comparison of the immediate versus delayed therapy of acute hepatitis C is important. Such studies should define whether delaying treatment avoids unnecessary therapy while not decreasing the overall rate of sustained response.

Natural History and Immunology. Therapeutic studies of acute hepatitis C provide an excellent venue for ancillary studies on the viral and immunopathogenesis of acute infection. In all studies of acute hepatitis C, there is a critical need for regular, scheduled, prolonged follow-up of treated patients, well beyond the 24 weeks after treatment, the period usually used in evaluating outcome in chronic hepatitis C. These studies are needed to more clearly define rates of complete and definitive resolution of infection. Furthermore, long-term clinical outcomes

should be modeled accurately in treated and untreated patients considering the low rate of clinically relevant chronic sequelae seen during the first 2 decades of infection with HCV. Nevertheless, if a near universal eradication of HCV can be achieved with interferon therapy during acute infection, it is difficult not to believe that this will translate into significant clinical benefit in most patients.

References

1. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Goa F, Moyer LA, Kaslow RA, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341:556-562.
2. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001; 345:41-52.
3. Orland JR, Wright TL, Cooper S. Acute hepatitis C. HEPATOLOGY 2001; 33:321-327.
4. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, Nolt K, et al. The natural history of hepatitis C virus infection: host viral, and environmental factors. JAMA 2000;284:450-456.
5. Alberti A, Chemello L, Benvegnù L. Natural history of hepatitis C. J Hepatol 1999;31:17-24.
6. Viladomiu L, Genesca J, Esteban JI, Allende H, Gonzalez A, Lopez-Talavera JC, Estaban R, et al. Interferon alpha in acute posttransfusion hepatitis C: a randomized, controlled trial. HEPATOLOGY 1992;15:767-769.
7. Lampertico P, Rumi M, Romeo R, Craxì A, Soffredini R, Biassoni D, Columbo M. A multicenter randomized controlled trial of recombinant interferon-alpha 2b in patients with acute transfusion-associated hepatitis C. HEPATOLOGY 1994;19:199-202.
8. 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;21:831-836.
9. Li XW, Zhu ZY, Dao WP, Liu FH, Die GS. A report on therapy of interferon alfa 2b in patients with acute hepatitis C. Chung Hua Nei Ko Tsa Chih 1993;32:409-411.
10. Omata M, Yokosuka O, Takano S, Kato N, Hosoda K, Imazeki F, Tada M. Resolution of acute hepatitis C after therapy with natural beta interferon. Lancet 1991;338:914-915.
11. Calleri G, Colombatto P, Gozzelino M, Chieppa F, Romano P, Delmastro B, Macor A, et al. Natural beta interferon in acute type-C hepatitis patients: a randomized controlled trial. Ital J Gastroenterol Hepatol 1998; 30:181-184.
12. Takano S, Satomura Y, Omata M. Effects of interferon beta on non-A, non-B acute hepatitis: a prospective, randomized, controlled-dose study. Japan Acute Hepatitis Cooperative Study Group. Gastroenterology 1994; 107:805-811.
13. Fabris P, Tositti G, Giordani MT, Infantolino D, De Lalla F. Three times weekly versus daily dose alpha-interferon treatment in patients with acute hepatitis C. Am J Gastroenterol 2002;97:492-493.
14. Alberti A, Chemello L, Belussi F, Pontisso P, Tisminetsky S, Gerotto M, Baralle F, et al. Outcome of acute hepatitis C and role of alpha interferon therapy. In: Nishioka KSH, Oda T, eds. Viral Hepatitis and Liver Disease. Tokyo, Japan: Springer-Verlag, 1994;604-606.
15. Ohnishi K, Nomura F, Nakano M. Interferon therapy for acute posttransfusion non-A, non-B hepatitis: response with respect to anti-hepatitis C virus antibody status. Am J Gastroenterol 1991;86:1041-1049.
16. Palmovic D, Kurelac I, Crnjakovic-Palmovic J. The treatment of acute post-transfusion hepatitis C with recombinant interferon-alpha. Infection 1994;22:222-223.
17. Tassopoulos NC, Koutelou MG, Papatheodoridis G, Polychronaki H, Delladetsima I, Giannikakis T, Todoulos A, et al. Recombinant human interferon alfa-2b treatment for acute non-A, non-B hepatitis. Gut 1993; 34(Suppl 2):S130-S132.
18. Gursoy M, Gur G, Arslan H, Ozdemir N, Boyacioglu S. Interferon therapy in haemodialysis patients with acute hepatitis C virus infection and factors that predict response to treatment. J Viral Hepat 2001;8:70-77.
19. Vogel W, Graziadei I, Umlauft F, Datz C, Hackl F, Alliger S, Grunewald K, et al. High dose interferon alpha 2b treatment prevents chronicity in acute hepatitis C. A pilot study. Dig Dis Sci 1996;41(Suppl 12):81S-85S.
20. 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 [Abstract]. Gastroenterology 2000;118:960A.
21. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, Pastore G, et al. Treatment of acute hepatitis C with interferon alpha-2b. N Engl J Med 2001;345:1452-1457.
22. Gerlach TJ, Zachoval R, Gruener N, Jung M-C, Ulsenheimer A, Schraut W, Schirren A, et al. Acute hepatitis C: natural course and response to antiviral treatment [Abstract]. HEPATOLOGY 2001;34:341A.
23. Poynard T, Regime C, Myers RP, Thevenot T, Leroy V, Mathurin P, Opolon P, et al. Interferon for acute hepatitis C (Cochrane Review). In: The Cochrane Library, Issue 1, Oxford, UK, 2002.
24. Giuberti T, Marin MG, Ferrari C, Marchelli S, Schianchi C, Antoni AM, Pizzocolo G, et al. Hepatitis C virus viremia following clinical resolution of acute hepatitis C. J Hepatol 1994;1004:666-671.
25. Kenny-Walsh E for the Irish Hepatology Research Group. Clinical outcomes after hepatitis infection from contaminated anti-globulin. N Engl J Med 1999;340:1228-1233.
26. Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. HEPATOLOGY 1999;29:908-914.
27. Cammà C, Craxì A. Interferon treatment for acute hepatitis C: a meta-analysis [Abstract]. HEPATOLOGY 2002 (in press).
28. Alberti A. Interferon therapy of acute hepatitis C. Viral Hepatitis Reviews 1995;1:37-45.
29. Hoofnagle JH. Therapy for acute hepatitis C. N Engl J Med 2001;345: 1495-1497.