

Katja Deterding, Heiner Wedemeyer,
and Michael P. Manns

Keywords

Acute HCV • Antiviral therapy • PEG-IFNa-2b

Introduction

The rate of chronicity in patients with acute hepatitis C is 50–90%. Early control of hepatitis C virus (HCV) infection by interferon alpha-based therapies has been shown to be possible in the majority of patients. Treatment of acute hepatitis C should be considered not only because chronic HCV infection can lead to further serious clinical sequelae like liver cirrhosis or hepatocellular carcinoma but also because HCV viremia may be associated with a risk for transmission of HCV to other persons and because hepatitis C can have significant social, legal, and economic consequences, especially for infected members of the health care system. While treatment of acute hepatitis C with type I interferons is well established, there has been considerable debate as to which therapy and which time point of therapy is optimal. To determine this we must consider efficacy,

side effects, cost, and whether the addition of ribavirin is necessary as it is when treating chronic hepatitis C infection [1].

Epidemiology and Natural Course of Acute Hepatitis C

The incidence of acute hepatitis C differs significantly between countries. HCV is highly endemic in some African countries. New HCV infections still occur in countries with a low human development index since only half of the blood products are screened for anti-HCV in these countries and about 40% of all injections are still given via re-used equipment. However, acute hepatitis C is also still present in Western countries. In Italy, the incidence ranges from 1 to 14 infections per 100,000 according to the national surveillance agency [2], the Italian blood donor program [3], or evaluation in the general population [4].

The cause of transmission of HCV is often difficult to define. Since screening of blood products for the HCV by PCR was introduced, the risk for transfusion-associated acute hepatitis C has been dramatically reduced. Thus, the main reason for HCV infection nowadays is intravenous drug use. The incidence in the high-risk group of drug abusers is up to 39/100 person

K. Deterding, MD • M.P. Manns, MD (✉)
Department of Gastroenterology, Hepatology,
and Endocrinology, Hannover Medical School,
Carl-Neuberg-Strasse 1, Hannover 30625, Germany
e-mail: manns.michael@mh-hannover.de

H. Wedemeyer, MD
Department of Gastroenterology,
Hannover Medical School, Hannover, Germany

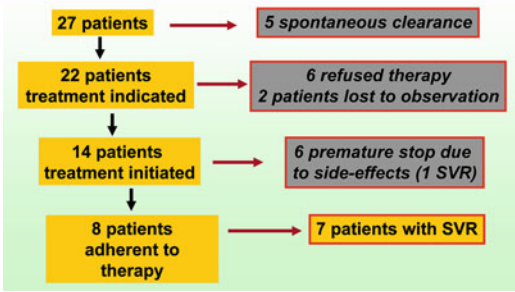


Fig. 2.1 Treatment of acute hepatitis C in IV drug addicts: The Swiss Association for the Study of the Liver Study (SASL 18). I.V. drug user from the Swiss HCV cohort showed rather low overall sustained response rates (based on data from ref. [6])

years [5]. Long-term IV drug users show HCV infection rates of 50–80%. However, IV drug users may be difficult to treat for acute hepatitis C as data from the Swiss HCV cohort showed rather low overall sustained response rates (Fig. 2.1). This was due to noncompliance, loss of follow up, and to prematurely stopping therapy in a significant number of patients [6]. On the other hand, Italian investigators reported much better experiences in treating acute hepatitis C [7] justifying treatment attempts in well-established settings of experienced physicians treating not only infectious diseases but also addiction and psychiatric disorders.

Other possible modes of acquisition are medical procedures, sexual intercourse, or needlestick injuries in health care professionals [8–11]. In particular the last group of patients may ask for immediate treatment of acute hepatitis C. Furthermore, the risk to acquire HCV after occupational exposure might be lower than previously reported (Fig. 2.2) [12].

HCV-RNA can be detectable in serum within 3–7 days after exposure. HCV-RNA levels rise rapidly during the first weeks followed by a rise of serum aminotransferases 2–8 weeks after exposure [13]. The elevation of serum alanine aminotransferase (ALT) indicating hepatic injury, inflammation, and necrosis commonly may reach levels greater than 10 times the upper limit of normal. Unfortunately, the serological development

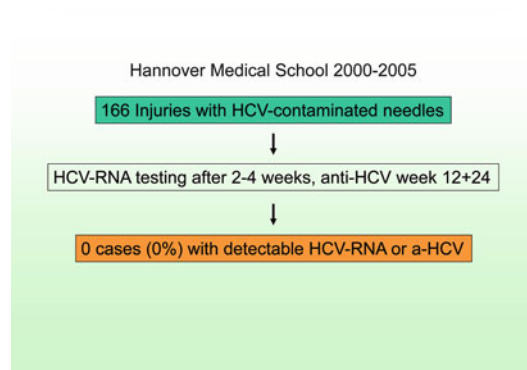


Fig. 2.2 Low rate of HCV seroconversion after occupational exposure to HCV (based on data from ref. [12])

of acute HCV infection is accompanied by clinical symptoms only in a minority of cases. Jaundice occurs in only 20–30% of patients, mostly between 2 and 12 weeks after infection [14, 15]. More commonly, nonspecific symptoms, such as fatigue, low-grade fever, myalgia, nausea, vomiting, or itching, are clinical correlates of the infection leading to high rates of unrecognized cases in the acute phase of the disease. It is quite well established that patients are more likely to recover spontaneously if they are symptomatic. We were able to show that young male patients with HCV genotype 3 infection recovered more than individuals infected with genotype 1 [16]. However, in other cohorts of patients with more severe symptoms, the HCV genotype failed to be significantly associated with recovery or chronicity. There is only limited data regarding how different factors, such as ALT levels, bilirubin levels, age, sex, or HCV genotype, are associated with the outcome of interferon treatment in acute hepatitis C. In the Hep-Net Acute HCV-II study, only baseline ALT levels of greater than 500 U/L but none of the other factors were associated with SVR to 6 months of PEG-IFN α -2b treatment (Fig. 2.3) [17]. Thus, patients with more severe hepatitis may require less stringent therapies and the natural course of the infection can be monitored for some time before treatment is initiated. Importantly, in none of the studies conducted to

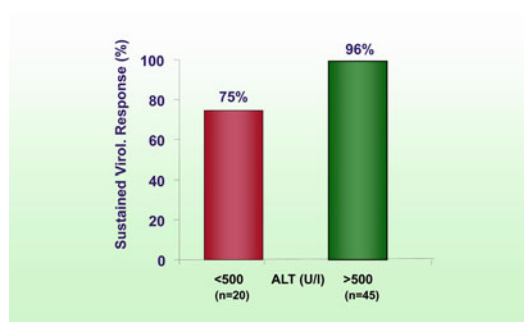


Fig. 2.3 Baseline ALT levels and treatment response in the Hep-Net Acute HCV-II study. In the Hep-Net Acute HCV-II Study, only baseline ALT levels of greater than 500 U/L but none of the other factors were associated with SVR to 6 months of PEG-IFN- α -2b treatment (based on data from ref. [17])

date was HCV genotype clearly associated with treatment outcome. This is significantly different than what is observed in patients with chronic HCV infection.

Conventional Recombinant Interferon Alpha for the Treatment of Acute Hepatitis C

Several small trials performed in the 90s indicated that HCV infection can be treated very effectively in its acute phase. Some of these studies were controlled [18–23], while others did not include a control group [24]. Most of these studies had substantial limitations. Some included only a limited number of patients [22, 24] or only individuals with transfusion-associated HCV infection [18–23]. The treatment schedules differed between the administered type of interferon, interferon dosage, and treatment duration. Therapeutic efficacy was not determined on the basis of HCV-RNA measurement in all studies [18, 23]. All but one study [21] indicated a beneficial effect of therapy. Higher doses of interferon seemed to be associated with better treatment response. In a trial by Vogel et al., 10 MU interferon alfa-2b daily achieved a virological response in 90% of cases after a

follow-up of 7–42 months [24]. Patients cleared HCV-RNA within 4–12 days. Aminotransferases normalized after 18–43 days of therapy. Thus, the results of the pilot studies indicated that virological response rates were dose dependent and increased with longer treatment duration. A daily administration of interferon seemed to be more effective than an intermittent dosage.

The treatment of 44 consecutive patients with acute hepatitis C published by Jäeckel et al. in 2001 received much attention [25]. Patients were treated for 24 weeks with an induction dosing of 5 MU interferon alfa-2b daily for 4 weeks followed by 3 MU interferon alfa-2b thrice weekly for additional 20 weeks. After 24 week follow-up, 98% of cases had undetectable HCV-RNA and normal ALT levels.

Thus, the study showed that progression to chronicity can be prevented by early treatment with interferon-based monotherapy. Importantly, no combination with ribavirin was necessary. A further follow-up showed that virological response rates were sustained for up to 224 weeks after the end of therapy [26].

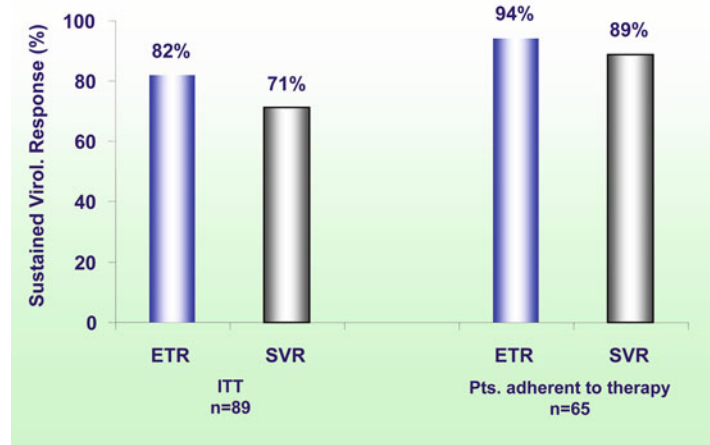
Subsequent studies from Belgium [27] and Japan [28] suggested that even shorter therapies of only 1–2 months with daily injections of interferon alpha might be possible leading to sustained response rates between 84 and 100% if treatment is initiated soon after the acute exposure.

Pegylated Interferon Alpha for the Treatment of Acute Hepatitis C

Pegylated interferons have been investigated by several investigators to treat acute hepatitis C. In 2005, Santantonio published on a cohort of 16 Italian patients with acute HCV treated with PEG-IFNa-2b for 24 weeks [29]. Sustained clearance of HCV-RNA was observed in 15 patients (94%). Treatment was initiated 12 weeks after the clinical onset of hepatitis. The proportion of individuals infected with HCV genotypes 2 or 3 was high (63%).

The fairly good tolerability and the high sustained response rate to PEG-IFNa-2b treatment

Fig. 2.4 Response rates in the Hep-Net Acute Study HCV-II. Virological response rates defined as undetectable HCV-RNA via polymerase chain reaction (<600 IU/mL). *ETR* end-of-treatment response; *SVR* sustained virological response (based on data from ref. [17])



of acute hepatitis C was confirmed by the German Hep-Net Acute HCV-II study [17]. Eighty-nine patients were recruited receiving at least one dose of PEG-IFNa-2b. Treatment was scheduled for 24 weeks and no ribavirin was given. This study reflects to a large extent the “real-life” setting in Germany since patients were recruited via the German network of excellence on viral hepatitis “Hep-Net” [30]. Subsequently, patients were included not only by 18 university hospitals but also by 26 municipal hospitals and even by nine gastroenterologists in private practice. Possible sources of infections were medical procedures, IV drug abuse, and sexual exposure accounting for about three-fifths of cases. Sixty-six percent of patients were infected with HCV genotype 1 and maximum ALT levels before treatment ranged between 24 and 3,399 U/L (median 599). The median time from the most likely date of infection to start of therapy was 76 days and the time from the onset of symptoms to the start of therapy ranged between 5 and 131 days with a median of 27 days. Thus, therapy was started 1–2 months earlier than in most of the other recent studies on acute hepatitis C where treatment was usually delayed until 3 months after the patient first presented.

The Hep-Net-Acute HCV-II study showed end-of-treatment and sustained virological

response rates of 82 and 71% in the intent-to-treat analysis, respectively (Fig. 2.4). Thus, response rates were lower than in several previous studies including the German Acute-HCV-I study using conventional interferon alpha [25]. However, only 70 patients fulfilled the so-called 80/80-criteria of adherence to therapy receiving at least 80% of the PEG-IFN dose and completing at least 80% of treatment duration. A rather high number of patients (15%) were lost to follow-up and protocol violations were performed in another four patients – possibly reflecting the high number of participating centers, including some rather inexperienced sites. Additionally, eight individuals had to stop treatment due to side effects and only four of those achieved an SVR. The sustained response in the group of patients who was adherent to therapy and completed follow-up ($n=65$) was 89%. These results are similar with that reported in other studies. As already mentioned earlier, only baseline ALT levels but not HCV genotype, HCV-RNA levels, age, or sex were associated with sustained response rate in this study.

Another study from Italy suggested that a PEG-IFNa-2b dose of at least 1.3 $\mu\text{g/kg}$ should be administered in acute hepatitis C since lower doses may reduce the chance to achieve a sustained response [31]. However, de Rosa and colleagues treated their patients for only 12 weeks.

None of the other studies treating acute hepatitis C for 24 weeks with PEG-IFNa-2b including the Swiss study on IV drug addicts [6] reported a similar dose effect.

Timing of Therapy; Early Treatment of Acute Hepatitis C or Delayed Treatment?

Data on the optimal timing of treatment for acute hepatitis C is limited since the various studies are difficult to compare and the general approach to delay treatment [32] has been defined as either 12 weeks after the acquisition of HCV or after the clinical onset of hepatitis. In a Japanese population, Nomura compared early “immediate” treatment to treatment starting 1 year following infection [28]. A superior result was achieved when treatment was initiated sooner after infection than waiting a full year after presumed exposure.

The Hep-Net-Acute-HCV-III study was designed in 2004 as a prospective, randomized study in patients with symptomatic acute hepatitis C comparing the efficacy and safety of immediate PEG-IFNa-2b treatment for 6 months vs. delayed treatment with PEG-IFNa-2b plus ribavirin for 6 months starting 12 weeks after randomization in patients who were still HCV-RNA positive. All asymptomatic patients were assigned to early treatment with PEG-IFNa-2b. A planned analysis of 108 patients randomized until December 31, 2007 confirmed that early immediate treatment with PEG-IFNa-2b was highly effective in both symptomatic and asymptomatic patients. Delayed IFNa+ribavirin treatment resulted in a lower overall response rate. However, patients who were adherent to the prescribed regimen had similar efficacy rates in symptomatic patients [33].

If frequent monitoring of HCV-RNA levels is possible, HCV-RNA kinetics may also be considered for timing therapy as repeated measurement of HCV-RNA may predict spontaneous clearance of acute hepatitis C [34].

Duration of Therapy

As mentioned earlier, most trials using pegylated interferon alpha-2b have treated patients for 24 weeks. However, shorter therapies are very likely to be possible [31], in particular, in individuals with baseline parameters being associated with a high likelihood to achieve a sustained response.

Ribavirin

The need for ribavirin is well established in the treatment of chronic hepatitis C. However, there appears to be no need to use ribavirin in patients with acute hepatitis C since approximately 90% of patients appear to achieve a sustained viral response with interferon alpha alone. Ribavirin can be associated with significant side effects and costs and thus, in our opinion combination therapy for acute hepatitis C is not justified. However, the addition of ribavirin can be considered in patients with delayed HCV-RNA kinetics after the onset of treatment, and in those patients with HCV genotype 1 and a low or normal baseline value for serum ALT value.

Influence of Interferon Alpha on Cellular Immune Responses in Acute Hepatitis C

Cellular immunity has been studied extensively in acute hepatitis C showing that HCV specific T-cell responses play an important role in the natural course of the infection. The adaptive T-cell response is mediated both by CD4+ helper T-cells and CD8+ killer T-cells. Involvement of CD 4+ lymphocytes in successful recovery of acute HCV infection was first proposed by Diepolder et al., who observed a strong proliferative immune response mainly against the NS3 protein and a significant production of interferon-gamma by HCV-specific CD4+ T-cells in patients with self-limited disease [35]. Thereafter, several groups consistently found an association between

a strong, multispecific and maintained HCV specific CD4+ und CD8+ T-cell response and the resolution of acute HCV infection [36].

CD4+ T-cells seem to be present for several years after recovery [37], there are conflicting data whether HCV-specific CD8+ T-cell responses persist [37] or decline [38] over time. However, several studies observed durable HCV-specific T-cells in HCV seronegative individuals, who were exposed to HCV by occupational exposure or as household members of HCV-positive partners, but who never became HCV-RNA positive [39]. These observations suggest that HCV-specific T-cells might be induced upon subclinical exposure and might contribute to protection against clinically apparent HCV infection.

Studies of interferon therapy on CD4+ und CD8+ T-cells in patients with acute HCV could not detect a clear relationship between treatment outcome and T-cell immunity [40–42]. Overall, HCV-specific cellular immunity in the peripheral blood cells seems to decline during and after interferon alpha-induced recovery. Possible explanations are that (1) interferon alpha has antiproliferative properties, which could prevent homeostatic and TCR-ligation-driven proliferation of T-cells and thus explain in part reduced frequency of HCV-specific T-cells and weaker proliferative responses; (2) interferon alpha may also have caused apoptosis of activated T-cells since interferon alpha sensitizes cells to antigen-induced cell death occurring at the end of an immune response; (3) HCV-specific T-cells may have disappeared from the circulation and homed to the primary site of inflammation, the liver. We have shown that the decline of T-cells during interferon alpha therapy may be a consequence of both, apoptosis and homing [43]. Thus, the balance between cell death vs. regulation of chemokine receptors potentially can lead to different long-term outcomes.

Conclusions

Interferon alpha therapy of acute hepatitis C is well established. Response rates are high and pegylated interferons can be recommended while

ribavirin administration is usually not required. Early immediate treatment with PEG-IFNa-2b is highly effective in both symptomatic and asymptomatic patients. Delayed IFNa+ribavirin treatment resulted in lower overall response rates. However, if patients who were adherent to treatment this strategy seems to be of similar efficacy in symptomatic patients. Asymptomatic patients with genotype 1 infection should be treated as early as possible while treatment might be delayed in individuals presenting with significant symptoms, at least 10 times elevated ALT levels and in patients with genotype 2 or 3 infections. Currently, we still would recommend a 24-week course of treatment although shorter treatment regimens are likely to be effective in a significant proportion of patients.

The optimal management of patients with acute hepatitis C infection should include a careful workup of clinical and virological data as well as the consideration of the individual patient's history.

References

1. Wedemeyer H, Jackel E, Wiegand J, Cornberg M, Manns MP. Whom? When? How? Another piece of evidence for early treatment of acute hepatitis C. *Hepatology*. 2004;39:1201–3.
2. Mele A, Tosti ME, Marzolini A, Moiraghi A, Ragni P, Gallo G, et al. Prevention of hepatitis C in Italy: lessons from surveillance of type-specific acute viral hepatitis. SEIEVA collaborating Group. *J Viral Hepat*. 2000;7:30–5.
3. Tosti ME, Solinas S, Prati D, Salvaneschi L, Manca M, Francesconi M, et al. An estimate of the current risk of transmitting blood-borne infections through blood transfusion in Italy. *Br J Haematol*. 2002;117: 215–9.
4. Kondili LA, Chionne P, Costantino A, Villano U, Lo NC, Pannozzo F, et al. Infection rate and spontaneous seroreversion of anti-hepatitis C virus infection during the natural course of hepatitis C virus infection in the general population. *Gut*. 2002;50:693–6.
5. Roy K, Hay G, Andragetti R, Taylor A, Goldberg D, Wiessing L. Monitoring hepatitis C virus infection among injecting drug users in the European Union: a review of the literature. *Epidemiol Infect*. 2002;129: 577–85.
6. Broers B, Helbling B, Francois A, Schmid P, Chuard C, Hadengue A, et al. Barriers to interferon-alpha therapy are higher in intravenous drug users than in other patients with acute hepatitis C. *J Hepatol*. 2005;42:323–8.

7. De Rosa FG, Bargiacchi O, Audagnotto S, Garazzino S, Cariti G, Veronese L, et al. The early HCV RNA dynamics in patients with acute hepatitis C treated with pegylated interferon-alpha2b. *Antivir Ther.* 2006;11:165–71.
8. Deterding K, Wiegand J, Gruner N, Wedemeyer H. Medical procedures as a risk factor for HCV infection in developed countries: do we neglect a significant problem in medical care? *J Hepatol.* 2008;48:1019–20.
9. Santantonio T, Medda E, Ferrari C, Fabris P, Cariti G, Massari M, et al. Risk factors and outcome among a large patient cohort with community-acquired acute hepatitis C in Italy. *Clin Infect Dis.* 2006;43:1154–9.
10. Prati D. Transmission of hepatitis C virus by blood transfusions and other medical procedures: a global review. *J Hepatol.* 2006;45:607–16.
11. Marti Nez-Bauer E, Fornis X, Armelles M, Planas R, Sola R, Vergara M, et al. Hospital admission is a relevant source of hepatitis C virus acquisition in Spain. *J Hepatol.* 2008;48(1):20–7.
12. Kubitschke A, Bader C, Tillmann HL, Manns MP, Kuhn S, Wedemeyer H. Injuries from needles contaminated with hepatitis C virus: how high is the risk of seroconversion for medical personnel really? *Internist (Berl).* 2007;48:1165–72.
13. Bertolotti A, Ferrari C. Kinetics of the immune response during HBV and HCV infection. *Hepatology.* 2003;38:4–13.
14. Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. *N Engl J Med.* 1992;327:1899–905.
15. Santantonio T, Sinisi E, Guastadisegni A, Casalino C, Mazzola M, Gentile A, et al. Natural course of acute hepatitis C: a long-term prospective study. *Dig Liver Dis.* 2003;35:104–13.
16. Lehmann M, Meyer MF, Monazahian M, Tillmann HL, Manns MP, Wedemeyer H. High rate of spontaneous clearance of acute hepatitis C virus genotype 3 infection. *J Med Virol.* 2004;73:387–91.
17. Wiegand J, Buggisch P, Boecher W, Zeuzem S, Gelbmann CM, Berg T, et al. Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study. *Hepatology.* 2006;43:250–6.
18. Viladomiu L, Genesca J, Esteban JI, Allende H, Gonzalez A, Lopez-Talavera JC, et al. Interferon-alpha in acute posttransfusion hepatitis C: a randomized, controlled trial. *Hepatology.* 1992;15:767–9.
19. 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.
20. Lampertico P, Rumi M, Romeo R, Craxi A, Soffredini R, Biassoni D, et al. A multicenter randomized controlled trial of recombinant interferon-alpha 2b in patients with acute transfusion-associated hepatitis C. *Hepatology.* 1994;19:19–22.
21. Calleri G, Colombatto P, Gozzelino M, Chieppa F, Romano P, Delmastro B, et al. Natural beta interferon in acute type-C hepatitis patients: a randomized controlled trial. *Ital J Gastroenterol Hepatol.* 1998;30:181–4.
22. Omata M, Yokosuka O, Takano S, Kato N, Hosoda K, Imazeki F, et al. Resolution of acute hepatitis C after therapy with natural beta interferon. *Lancet.* 1991; 338:914–5.
23. 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;86:1041–9.
24. Vogel W, Graziadei I, Umlauf F, Datz C, Hackl F, Allinger S, et al. High-dose interferon-alpha2b treatment prevents chronicity in acute hepatitis C: a pilot study. *Dig Dis Sci.* 1996;41:81S–5.
25. Jäeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med.* 2001;345: 1452–7.
26. Wiegand J, Jackel E, Cornberg M, Hinrichsen H, Dietrich M, Kroeger J, et al. Long-term follow-up after successful interferon therapy of acute hepatitis C. *Hepatology.* 2004;40:98–107.
27. Delwaide J, Bourgeois N, Gerard C, De Maeght S, Mokaddem F, Wain E, et al. Treatment of acute hepatitis C with interferon alpha-2b: early initiation of treatment is the most effective predictive factor of sustained viral response. *Aliment Pharmacol Ther.* 2004;20:15–22.
28. Nomura H, Sou S, Tanimoto H, Nagahama T, Kimura Y, Hayashi J, et al. Short-term interferon-alfa therapy for acute hepatitis C: a randomized controlled trial. *Hepatology.* 2004;39:1213–9.
29. Santantonio T, Fasano M, Sinisi E, Guastadisegni A, Casalino C, Mazzola M, et al. Efficacy of a 24-week course of PEG-interferon alpha-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. *J Hepatol.* 2005;42:329–33.
30. Manns MP, Meyer S, Wedemeyer H. The German network of excellence for viral hepatitis (Hep-Net). *Hepatology.* 2003;38:543–4.
31. De Rosa FG, Bargiacchi O, Audagnotto S, Garazzino S, Cariti G, Raiteri R, et al. Dose-dependent and genotype-independent sustained virological response of a 12 week pegylated interferon alpha-2b treatment for acute hepatitis C. *J Antimicrob Chemother.* 2006;57:360–3.
32. Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology.* 2003;125:80–8.
33. Deterding K, Gruner N, Wiegand J, Buggisch P, Galle P, Spengler U, et al. Early versus delayed treatment of acute hepatitis C: The German HEP-NET acute HCV-III study—a randomized controlled trial. *J Hepatol.* 2009;50:380.
34. Hofer H, Watkins-Riedel T, Janata O, Penner E, Holzmann H, Steindl-Munda P, et al. Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. *Hepatology.* 2003;37:60–4.

35. Diepolder HM, Zachoval R, Hoffmann RM, Wierenga EA, Santantonio T, Jung MC, et al. Possible mechanism involving T-lymphocyte response to non-structural protein 3 in viral clearance in acute hepatitis C virus infection. *Lancet*. 1995;346:1006–7.
36. Rehermann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat Rev Immunol*. 2005;5:215–29.
37. Takaki A, Wiese M, Maertens G, Depla E, Seifert U, Liebetrau A, 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.
38. Chang KM, Thimme R, Melpolder JJ, Oldach D, Pemberton J, Moorhead-Loudis J, et al. Differential CD4(+) and CD8(+) T-cell responsiveness in hepatitis C virus infection. *Hepatology*. 2001;33: 267–76.
39. Kubitschke A, Bahr MJ, Aslan N, Bader C, Tillmann HL, Sarrazin C, et al. Induction of hepatitis C virus (HCV)-specific T cells by needle stick injury in the absence of HCV-viraemia. *Eur J Clin Invest*. 2007; 37:54–64.
40. Tester I, Smyk-Pearson S, Wang P, Wertheimer A, Yao E, Lewinsohn DM, et al. Immune evasion versus recovery after acute hepatitis C virus infection from a shared source. *J Exp Med*. 2005;201:1725–31.
41. Rahman F, Heller T, Sobao Y, Mizukoshi E, Nascimbeni M, Alter H, et al. Effects of antiviral therapy on the cellular immune response in acute hepatitis C. *Hepatology*. 2004;40:87–97.
42. Lauer GM, Lucas M, Timm J, Ouchi K, Kim AY, Day CL, et al. Full-breadth analysis of CD8+ T-cell responses in acute hepatitis C virus infection and early therapy. *J Virol*. 2005;79:12979–88.
43. Wiegand J, Cornberg M, Aslan N, Schlaphoff V, Sarrazin C, Kubitschke A, et al. Fate and function of hepatitis-C-virus-specific T-cells during peginterferon-alpha2b therapy for acute hepatitis C. *Antivir Ther*. 2007;12:303–16.

<http://www.springer.com/978-1-4614-1191-8>

Chronic Hepatitis C Virus

Advances in Treatment, Promise for the Future

Shiffman, M.L. (Ed.)

2012, XVI, 332 p. 53 illus., 33 illus. in color., Hardcover

ISBN: 978-1-4614-1191-8