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BRIEF ARTICLE

Sustained virological response: A milestone in the treatment of chronic hepatitis C

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Abstract

AIM: To evaluate the long-term eradication of hepatitis C virus (HCV) infection and liver-related complications in chronically infected patients that have achieved sustained virological response.

METHODS: One hundred and fifty subjects with chronic hepatitis C (CHC) or cirrhosis and sustained virological response (SVR) between the years of 1989 and 2008 were enrolled in a long-term clinical follow-up study at the Gastrointestinal and Liver Unit of the University Hospital of Naples "Federico Ⅱ". At the beginning of the study, the diagnosis of HCV infection was made on the basis of serum positivity for antibodies to HCV and detection of HCV RNA transcripts, while a diagnosis of chronic hepatitis was formulated using imaging techniques and/or a liver biopsy. SVR was achieved by interferon-based therapy, both conventional and pegylated, with and without ribavirin treatment. The patients were evaluated for follow-up at a median length of 8.6 years, but ranged from 2-19.9 years. Among them, 137 patients had pre-treatment CHC and 13 had cirrhosis. The patients were followed with clinical, biochemical, virological, and ultrasound assessments on a given schedule. Finally, a group of 27 patients underwent a liver biopsy at the beginning of the study and transient elastography at their final visit to evaluate changes in liver fibrosis.

RESULTS: The median follow-up was 8.6 years (range 2-19.9 years). HCV RNA remained undetectable in all patients, even in patients who eventually developed liver-related complications, indicating no risk of HCV recurrence. Three liver-related complications were observed: two cases of hepatocellular carcinoma and one case of bleeding from esophageal varices resulting in an incidence rate of 0.23%/person per year. Further, all three complications took place in patients diagnosed with cirrhosis before treatment began. Only one death due to liver-related causes occurred, resulting in a mortality rate of 0.077% person per year. This amounts to a 99.33% survival rate in our cohort of patients after therapy for HCV infection. Finally, of the 27 patients who underwent a liver biopsy at the beginning of the study, a reduction in liver fibrosis was observed in 70.3% of the cases; only three cases registering values of liver stiffness indicative of significant fibrosis.

CONCLUSION: Patients with CHC and SVR show an excellent prognosis with no risk of recurrence and a very low rate of mortality. Our data indicate that virus-eradication following interferon treatment can last up to 20 years.

Key words: Antiviral therapy; Cirrhosis; Hepatitis C virus; Sustained virological response; Fibrosis

Core tip: This study represents one of the longest follow-up studies on the natural history of successfully treated chronically hepatitis C virus (HCV) infected individuals. The outcome of the study was very positive, as it revealed an extremely high survival rate, an extremely low rate of liver complications, and a significant reduction in liver fibrosis in patients who have achieved sustained virological response (SVR). All of the patients without cirrhosis before starting the treatment showed no signs of evolution or decompensation over the years of observation, proving that SVR positively changes the natural history in individuals with HCV-infection.

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INTRODUCTION

Hepatitis C virus (HCV) infection represents a serious challenge to global health, with an estimated 170 million carriers worldwide[1]. A significant complication in chronically infected individuals is the development of liver inflammation and fibrosis, which may progress to liver cirrhosis and hepatocellular carcinoma (HCC)[2-10].

For nearly 20 years, interferon-based therapy has been the standard therapy for chronic hepatitis C (CHC), with the optimal treatment of the combination of pegylated-interferon and ribavirin dating back ten years. The primary goal of HCV treatment is to achieve a sustained virological response (SVR). SVR is defined by undetectable HCV RNA levels 24 wk after completing treatment[11]. The achievement of the SVR in patients with CHC represents a milestone because it has been associated with the eradication of the infection, improvement in liver histology, improvement in quality of life, and reduced risk of cirrhosis and hepatocellular carcinoma[12-15]. Short term SVR in patients with chronic HCV-infection is well established, however, knowledge regarding long-term SVR remains to be elucidated. There are limited long-term studies observing chronically infected patients who have achieved SVR, all with a limited number of patients[12,16]. Further, studies that do have a large cohort of patients have a fairly short follow-up period[17,18]. Finally, the data gathered thus far lack real world examples as data gathered by subjects with SVR are usually limited to those participating in pivotal clinical trials.

The aim of this study was to evaluate the long-term outcomes of patients who obtain a SVR after antiviral therapy, regardless of the type treatment, in a monocentric cohort of patients representing a real world population with CHC during the last 20 years.

MATERIALS AND METHODS

Patients

From January 1989 to April 2008, 150 HCV-positive patients who achieved SVR after interferon-based therapy at the Gastroenterology Unit of the University of Naples "Federico Ⅱ" were enrolled in this cohort study. There were 100 men and 50 women (mean age, 56.37 ± 12.05 years; range 22-67 years). The main characteristics of our study population at baseline are reported in Table 1.

In this cohort, 137/150 (91.3%) patients had chronic hepatitis and 13 had liver cirrhosis. Before treatment, 21 patients had normal alanine transaminase (ALT) values and 129/150 (86%) had elevated ALT values ranging between 1.2 and 15.87 times the upper normal limit. A histological examination was performed in 103/150 (68.6%) of patients at baseline, while 47/150 (31.3%) patients refused the biopsy procedure and 27 patients showed comorbidities (Table 1). Nine patients had a diagnosis of arterial hypertension and two had an incomplete right bundle branch block. One patient had a medical history of previous angina pectoris and another suffered from a previous myocardial infarction, however, there was no cardiologic contraindication at the time the therapy started. Seven patients had thyroid disease; two patients had type Ⅱ diabetes; two had gastroesophageal reflux disease, and two had a co-infection of hepatitis B. One patient had a history of non-Hodgkin lymphoma that had been in remission for five years since the time the antiviral therapy started.

Modality of diagnosis

The diagnosis of HCV infection was made on the basis of serum positivity for antibodies to HCV and detection of HCV RNA transcripts. The diagnosis of chronic hepatitis was formulated by a histological assessment and scored according to the internationally accepted criteria[19]. The liver biopsy was not performed if the patients refused the procedure or had evidence of clinical, biochemical, ultrasound and endoscopic signs of liver cirrhosis. Transient elastography (TE), a non-invasive method of quantifying fibrosis developed as an alternative to liver biopsy, was carried out using FibroScan. Ultrasound elastography analyzes ultrasound frequency waves related to the elasticity (deforming capacity) of the liver. The methodology is simple, highly reproducible and can be completed in ten minutes. The diagnostic accuracy of TE is not as high as a liver biopsy, which remains the gold standard for evaluation of fibrosis. Nonetheless, in this context, TE is both highly sensitive and specific (79%-83% and 83%-89%, respectively)[20].

Therapy schedules

All patients were treated with interferon-based therapy,

Table 1 Baseline characteristics of 150 chronically infected hepatitis C virus patients with sustained virological response

Patients	150
Gender	
Male	100
Female	50
Patients with histological assessment[20]	103
Mild hepatitis (G0-G4)	52
Moderate hepatitis (G5-G9)	44
Severe hepatitis (G10-G18)	5
Staging S0-S1	44
Staging S2	25
Staging S3	10
Staging S4-S5	9
Cirrhosis S6	2
Genotype	
1a	14
1b	75
2	54
3	5
4	2
Comorbidity	
Cardiovascular diseases	13
Thyroid diseases	7
Crohn's disease	1
GERD	2
Diabetes mellitus type 2	2
HBV co-infection	2

GERD: Gastroesophageal reflux disease; HBV: Hepatitis B virus.

either in mono-therapy or in combination with ribavirin. Sixty-six subjects received conventional interferon mono-therapy. Twenty-five patients were treated with conventional interferon plus ribavirin and 59 patients were treated with pegylated interferon plus ribavirin. Conventional interferon was used at doses ranging between 3 and 6 MU every 2 d for a mean period of 49 ± 3.12 wk. The treatment regimen with pegylated interferon was carried out by international guideline recommendations and method indicated in the relevant product data sheets (Pegasys® 180 μg once weekly, subcutaneously; Pegintron® 1.5 μg/kg per week, subcutaneously; ribavirin 800, 1000 or 1200 mg/week orally, depending on body weight and virus genotype). The mean duration of the therapy was 47 ± 13 wk.

Follow-up

All patients were followed and analyzed for clinical, biochemical, virological and ultrasound parameters. All assessments were performed every 6 mo for the first two years of observation. In patients with cirrhosis at baseline, we continued to perform sequential clinical, biochemical and ultrasound follow-up every 6 mo, while the same panel of tests was conducted once a year in patients without cirrhosis. HCV RNA assessment was performed once per year during follow-up for all patients and whenever a decompensation or a progression of the liver disease occurred. At each medical visit, life-sign assessments and potential therapy-adverse effects were investigated. Biochemical evaluations measuring haemocrome (blood count), transaminases, bilirubin, alkaline phosphatase and renal function were performed. All patients underwent abdominal ultrasound every 6 mo. If a new space-occupying lesion was suspected, it was first analyzed by ultrasonography to determine if it was unquestionably benign (*e.g.*, cysts or hemangioma). If necessary, the lesion was further examined by computed tomography, magnetic resonance imaging, arteriography, or liver biopsy. In a group of 27 patients with liver biopsy at baseline, liver stiffness was assessed during the last visit. During this follow-up, cirrhotics were considered to have progression if they showed any of the following findings: ascites, bleeding varices, hepatic encephalopathy and HCC. The diagnosis of HCC was formulated using imaging techniques and/or biopsy, according to the Barcelona Clinical Liver Cancer standardized staging system for hepatocellular carcinoma[21].

Laboratory analysis

Serum was collected for detection of HCV RNA once per year after SVR was obtained. Qualitative detection of HCV-RNA was performed by a standardized qualitative assay, Cobas AmpliPrep/Cobas Taqman (CAP/CTM). This assay is based on the reverse transcription-polymerase chain reaction (RT-PCR) method, followed by HCV RNA real-time fluorescent detection from 850 μL of serum. HCV RNA concentration was read in IU/mL. The CAP/CTM assay has a sensitivity of 15 IU/mL, with a linear quantification range of 43-6.9 × 10^7 IU/mL.

RESULTS

Follow-up

The median duration of follow-up was 8.6 years (range 2-19.9 years). One hundred and fifteen/150 (76.6%) patients were followed for more than 4 years. Fifty-two/150 (34.6%) patients were followed for more than 10 years.

Virological outcomes

Zero of the 150 patients had a recurrence of HCV infection during the follow-up period. HCV RNA was evaluated in all patients with CAP/CTM assay, using at least four blood samples taken in different times (including the last sample available for each patient). No patient had detectable HCV-RNA in serum by RT-PCR in any sample, even in the patients who developed liver-related complications.

Survival and complication rates

The results from this study indicate the risk of liver-related death was only 0.67%, as only one patient died from liver-related causes. In addition, liver-related complications were observed in only three patients with a global complication incidence rate of 2%, while the complication incidence/person per year was 0.08%. These three complications included two patients with HCCs and one patient experiencing bleeding from esophageal varices. All three patients who developed complications had pre-treatment cirrhosis. Both patients who developed HCC were males, aged 61 developing the complication

Table 2 Liver fibrosis with paired assessment at baseline *vs* the end of follow-up

Baseline			End of follow-up		
Patients	METAVIR score	Corresponding value of LS (21) (kPa)	Mean value (range) of LS (kPa)	Mean follow-up (yr)	Patients with fibrosis regression
1	F0	< 6	5.9	10.6	0
18	F1	6.5 ± 1.1	5.4 (2.8-6.3)	9.48	13
6	F2	7.3 ± 1.4	6.2 (4.0-8.8)	6.02	4
0	F3	10.2 ± 1.9	-	-	-
1	F4	15 ± 4.1	6.8	8.3	1
1	Clinical cirrhosis	10.3	19.9	1	0

LS: Liver stiffness.

five years after follow-up, and aged 65 developing the complication nine years after follow-up, respectively. The 65-year-old male eventually died from liver-related complications. A 66-year-old female patient developed esophageal 17 bleeding years after the follow-up.

Regression of liver fibrosis

During the final visit, we performed TE on 27 patients who underwent a liver biopsy at baseline. The histological staging at baseline and the mean values of liver stiffness at the end of follow-up are reported in Table 2. Only in three cases were the values of liver stiffness higher than 7.3 kPa, the threshold indicative of significant fibrosis (F2 according to Metavir score). None of the patients had a liver stiffness score higher than 14.5 kPa, suggestive of cirrhosis. We observed regression of the fibrosis in 19/27 patients (70% of the cases).

DISCUSSION

The aim of this study was to assess the long-term effect of antiviral treatment in a large cohort of patients chronically infected with hepatitis C who had achieved SVR. This is one of the largest and longest studies on the natural history of successfully treated patients with chronic HCV infection in a real world setting. In the majority of the cases reported in the literature, the median follow-up duration is less than 5 years. In our study however, we observed 50 patients for up to 10 years and 21 patients for up to 15 years, with the median duration of the follow-up being 8.6 years. Overall, the clinical outcome of this study was very positive, indicating that prognosis in patients who obtained SVR is extremely promising.

The overall hepatic complication rate in our population was only 2%; a figure that is in agreement with other studies. Veldt *et al*[22] reported 3 cases of HCC in a population of 142 patients (2%) with SVR and a baseline fibrosis score that ranged between 4 and 6 according to the Ishak index[19]. Turner *et al*[23] reported 2 cases of HCC in a population of 152 patients (1.3%) with SVR and no cirrhosis. Ikeda *et al*[24] reported 30 cases of HCC in a population of 1097 patients (2.7%), of which 97 had cirrhosis and obtained SVR; but it was a retrospective, multicentric study with a median follow-up of 4.6 years. The high survival rate observed in our study (99.3%) is very consistent with values observed by George *et al*[18] (99.4%) and Imazeki *et al*[25] (99.97%).

We could not detect HCV-specific RNA transcripts in any of the patients at each follow-up, confirming that a durable SVR can be achieved with both conventional and pegylated interferon treatment[7-9]. Although a low rate of HCV-recurrence detected through RT-PCR assays has been reported, these data are in agreement with more recent studies on the topic[26-28]. The sensitivity of laboratory assays for HCV RNA detection has significantly increased throughout the years, and we can hypothesize that low serum levels of HCV RNA may not have been detected by a low sensitivity assay in the past, leading to a misclassification of SVR subjects. In fact, 5%, 9.7%, and 8% rates of HCV recurrence have been observed in previous studies[26-28]. In our study, HCV RNA was assessed through the most sensitive assay available (RT-PCR with sensitivity < 50 IU/mL). This sensitivity adds validity to our hypothesis that the hepatic complications observed in patients in our study were not directly related to ongoing HCV replication, but rather other complicating factors.

Of the 27 patients where fibrosis was evaluated, no patient with pre-treatment chronic hepatitis showed progression to cirrhosis, including those with advanced fibrosis (Ishak score 3-4/6). Moreover, a regression of fibrosis was reported in 70% of the cases. These results correlate well with the work by Poynard *et al*[29] showing that SVR (regardless of the therapy with which it is obtained) not only stops liver damage progression, but can also induce its regression. In this cohort, 1904 patients with CHC and SVR and with paired pre-treatment and post-treatment biopsies were observed; 86% of patients showed an improvement in fibrosis stage while 12% showed no change, even when the mean time between biopsies was only 20 mo[29]. Our data also comply with two recent studies with mean follow-up times of 5 and 6.5 years reporting 83% and 61% rates of fibrosis regression, respectively[18,30]. In these studies, the regression of fibrosis was assessed through liver biopsy. Although a liver biopsy is considered the gold standard; it does have limitations including sampling errors and interpretation of results influenced by intra- and inter-observer variation, implying that distinguishing real changes in fibrosis, longitudinally, is a difficult task[31]. Ellis *et al*[32] suggested that the most convincing evidence for regression of liver fibrosis derives from large-scale studies on post-treatment natural history. In fact, long-term follow-up studies indicate that regression of liver fibrosis is

associated with improved clinical outcomes, strengthening the perception that histological regression is a real phenomenon. Even though there is no universal parameter to define fibrosis regression, it is suggested that a long term assessment of clear clinical outcomes combined with non-invasive testing for fibrosis could help with the interpretation of the results[32].

In conclusion, our study documents that progression of liver damage and HCV infection relapse are virtually non-existent in patients with chronic hepatitis C infection who have achieved sustained virological response. Further, patients with pre-treatment evidence of cirrhosis show a rate of complications that cannot be neglected, but are hypothesized to occur due to complicating factors separate from HCV infection.

COMMENTS

Background

Sustained virological response (SVR) is by defined by undetectable hepatitis C virus (HCV) RNA levels 24 wk after completing treatment. The achievement of the SVR in patients with chronic hepatitis C (CHC) represents a milestone because it has been associated with the eradication of the infection, improvement in liver histology, improvement in quality of life, and reduced risk of cirrhosis and hepatocellular carcinoma. Short term SVR in patients with chronic HCV-infection is well established, however, knowledge regarding long-term SVR remains to be elucidated. There are limited long-term studies observing chronically infected patients who have achieved SVR, all with a limited number of patients.

Innovations and breakthroughs

This study represents one of the longest follow-up studies on the natural history of successfully treated chronically HCV infected individuals. The outcome of the study was very positive, as it revealed an extremely high survival rate, an extremely low rate of liver complications, and a significant reduction in liver fibrosis in patients who have achieved SVR.

Applications

The aim of this study was to evaluate the long-term outcomes of patients who obtain a SVR after antiviral therapy, regardless of the type treatment, in a monocentric cohort of patients representing a real world population with CHC during the last 20 years.

Peer review

It is a well planned study with sound methodology.

REFERENCES

1 **World Health Organization**. Hepatitis C- global prevalence (update). Available from: URL: http: //www.who.int/docstore/wer/pdf/2000/wer7503.pdf

2 **Nishiguchi S**, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, Shiomi S, Seki S, Kobayashi K, Otani S. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995; **346**: 1051-1055 [PMID: 7564784 DOI: 10.1016/S0140-6736(95)91739-X]

3 **Yoshida H**, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med* 1999; **131**: 174-181 [PMID: 10428733]

4 **Poynard T**, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. *Lancet* 2003; **362**: 2095-2100 [PMID: 14697814 DOI: 10.1016/S0140-6736(03)15109-4]

5 **Yoshida H**, Tateishi R, Arakawa Y, Sata M, Fujiyama S, Nishiguchi S, Ishibashi H, Yamada G, Yokosuka O, Shiratori Y, Omata M. Benefit of interferon therapy in hepatocellular carcinoma prevention for individual patients with chronic hepatitis C. *Gut* 2004; **53**: 425-430 [PMID: 14960528 DOI: 10.1136/gut.2003.030353]

6 **Lavanchy D**. The global burden of hepatitis C. *Liver Int* 2009; **29** Suppl 1: 74-81 [PMID: 19207969 DOI: 10.1111/j.1478-3231.2008.01934.x]

7 **Bruno S**, Facciotto C. The natural course of HCV infection and the need for treatment. *Ann Hepatol* 2008; **7**: 114-119 [PMID: 18626427]

8 **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 [PMID: 10895429 DOI: 10.1055/s-2000-9505]

9 **Ascione A**, Tartaglione T, Di Costanzo GG. Natural history of chronic hepatitis C virus infection. *Dig Liver Dis* 2007; **39** Suppl 1: S4-S7 [PMID: 17936222 DOI: 10.1016/S1590-8658(07)80003-X]

10 **Poynard T**, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; **349**: 825-832 [PMID: 9121257]

11 **Formann E**, Steindl-Munda P, Hofer H, Jessner W, Bergholz U, Gurguta C, Ferenci P. Long-term follow-up of chronic hepatitis C patients with sustained virological response to various forms of interferon-based anti-viral therapy. *Aliment Pharmacol Ther* 2006; **23**: 507-511 [PMID: 16441471 DOI: 10.1111/j.1365-2036.2006.02785.x]

12 **Tsuda N**, Yuki N, Mochizuki K, Nagaoka T, Yamashiro M, Omura M, Hikiji K, Kato M. Long-term clinical and virological outcomes of chronic hepatitis C after successful interferon therapy. *J Med Virol* 2004; **74**: 406-413 [PMID: 15368524 DOI: 10.1002/jmv.20190]

13 **Hung CH**, Lee CM, Lu SN, Wang JH, Hu TH, Tung HD, Chen CH, Chen WJ, Changchien CS. Long-term effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *J Viral Hepat* 2006; **13**: 409-414 [PMID: 16842444 DOI: 10.1111/j.1365-2893.2005.00707.x]

14 **Arase Y**, Ikeda K, Suzuki F, Suzuki Y, Saitoh S, Kobayashi M, Akuta N, Someya T, Koyama R, Hosaka T, Sezaki H, Kobayashi M, Kumada H. Long-term outcome after interferon therapy in elderly patients with chronic hepatitis C. *Intervirology* 2007; **50**: 16-23 [PMID: 17164553 DOI: 10.1159/000098958]

15 **Annicchiarico BE**, Siciliano M, Avolio AW, Grillo RL, Bombardieri G. A 5-year prospective study of the late resolution of chronic hepatitis C after antiviral therapy. *Aliment Pharmacol Ther* 2007; **25**: 1039-1046 [PMID: 17439504 DOI: 10.1111/j.1365-2036.2007.03295.x]

16 **Koh C**, Heller T, Haynes-Williams V. Clinical, virological, biochemical outcomes after 20 years of sustained virological response (SVR) in chronic hepatitis C: The NIH experience. 61th Annual Meeting of the American Association for the Study of Liver Diseases. Available from: URL: http: //www.natap.org/2010/AASLD/AASLD_25.htm

17 **Swain MG**, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, Dieterich DT, Abergel A, Pessôa MG, Lin A, Tietz A, Connell EV, Diago M. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology* 2010; **139**: 1593-1601 [PMID: 20637202 DOI: 10.1053/j.gastro.2010.07.009]

18 **George SL**, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. *Hepatology* 2009; **49**: 729-738 [PMID: 19072828 DOI: 10.1002/hep.22694]

19 **Ishak K**, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; **22**: 696-699 [PMID: 7560864 DOI: 10.1016/0168-8278(95)80226-6]

20 **Tsochatzis EA**, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol* 2011; **54**: 650-659 [PMID: 21146892 DOI: 10.1016/j.jhep.2010.07.033]

21 **Llovet JM**, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]

22 **Veldt BJ**, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HL. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007; **147**: 677-684 [PMID: 18025443]

23 **Turner AJ**, Hick PE. Inhibition of aldehyde reductase by acidic metabolites of the biogenic amines. *Biochem Pharmacol* 1975; **24**: 1731-1733 [PMID: 16 DOI: 10.1080/00365520510015467]

24 **Ikeda M**, Fujiyama S, Tanaka M, Sata M, Ide T, Yatsuhashi H, Watanabe H. Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C after sustained response to interferon. *J Gastroenterol* 2005; **40**: 148-156 [PMID: 15770398 DOI: 10.1007/s00535-004-1519-2]

25 **Imazeki F**, Yokosuka O, Fukai K, Saisho H. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. *Hepatology* 2003; **38**: 493-502 [PMID: 12883494 DOI: 10.1053/jhep.2003.50329]

26 **Marcellin P**, Boyer N, Gervais A, Martinot M, Pouteau M, Castelnau C, Kilani A, Areias J, Auperin A, Benhamou JP, Degott C, Erlinger S. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. *Ann Intern Med* 1997; **127**: 875-881 [PMID: 9382365]

27 **Cammà C**, Di Marco V, Lo Iacono O, Almasio P, Giunta M, Fuschi P, Vaccaro A, Fabiano C, Magrin S, Di Stefano R, Bonura C, Pagliaro L, Craxì A. Long-term course of interferon-treated chronic hepatitis C. *J Hepatol* 1998; **28**: 531-537 [PMID: 9566819 DOI: 10.1016/S0168-8278(98)80274-2]

28 **Reichard O**, Glaumann H, Frydén A, Norkrans G, Wejstål R, Weiland O. Long-term follow-up of chronic hepatitis C patients with sustained virological response to alpha-interferon. *J Hepatol* 1999; **30**: 783-787 [PMID: 10365802 DOI: 10.1016/S0168-8278(99)80129-9]

29 **Poynard T**, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, Ling MH, Albrecht J. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002; **122**: 1303-1313 [PMID: 11984517 DOI: 10.1053/gast.2002.33023]

30 **D'Ambrosio R**, Aghemo A, Rumi MG, Ronchi G, Donato MF, Paradis V, Colombo M, Bedossa P. A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. *Hepatology* 2012; **56**: 532-543 [PMID: 22271347 DOI: 10.1002/hep.25606]

31 **Bedossa P**, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003; **38**: 1449-1457 [PMID: 14647056 DOI: 10.1016/S0270-9139(03)80411-1]

32 **Ellis EL**, Mann DA. Clinical evidence for the regression of liver fibrosis. *J Hepatol* 2012; **56**: 1171-1180 [PMID: 22245903 DOI: 10.1016/j.jhep.2011.09.024]

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