Published in final edited form as:

Clin Gastroenterol Hepatol. 2009 February ; 7(2): 128–124. doi:10.1016/j.cgh.2008.07.017.

Hepatitis C in the Elderly: Epidemiology, Natural History and Treatment

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Abstract

Hepatitis C continues to be a major public health problem affecting approximately 3% of the global population (1). According to the World Health Organization, an estimated 170 million people have chronic hepatitis C (1). Ten to 20% of those who are chronically infected with chronic hepatitis C will progress to cirrhosis and 5% will develop hepatocellular carcinoma (1). Although the safety and efficacy of hepatitis C therapies have been extensively studied in patients between ages of 18 and 65, patients who are over 65 still remain an understudied and difficult to treat population. This review discusses the epidemiology, natural history and treatment of chronic hepatitis C in older adults.

EPIDEMIOLOGY

The prevalence of hepatitis C (HCV) infection in the elderly varies among different studies. According to one study that included 21,241 participants of the National Health and Nutrition Examination Survey III (NHANES III), the prevalence of positive HCV antibody was found to be 0.9% and 1.0% in subjects who were in the age group of 60–69 and ≥ 70 , respectively (2). Importantly, the prevalence of HCV antibody was significantly higher among the non-hispanic blacks who were in these age groups, with 60–69 and ≥ 70 with a prevalence of 2.5% (95% CI 1.8–3.4) and 2.8% (95% CI 1.4–5.4), respectively (2).

In another study that analyzed data from the NHANES, HCV RNA was detected in 87.4% of individuals who were 60 or older with history of abnormal serum alanine aminotransferase or blood transfusions before 1992 (3). Among the subjects aged 60 years or older, there was a significant association between HCV antibody positivity and being non-hispanic black as well as having history of blood transfusion before 1992, with odds ratios of 4.3 and 4.9, respectively (3).

In a study that was done in Italy among 496 elderly with a mean age of 79.31, the prevalence of positive HCV antibody was found to be around 11% (4). HCV antibody positivity was significantly associated with being between ages of 70 and 79 (OR= 8.02, $p < 0.001$), hepatitis B surface antibody positivity and/or hepatitis B core antibody positivity (OR= 4.00, $p < 0.001$) and female gender (OR= 2.86, $p < 0.005$) (4).

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Conflict of Interest Statement: None of the authors has conflict of interest in connection with the submitted manuscript.

In another Italian study, the prevalence of positive HCV antibody was reported to be 3.3% among 1063 people aged 60 years or older (5). From those who were positive for HCV antibody, 19 subjects (54.3%) had detectable HCV RNA (5). HCV genotype 2a was the most common genotype among those who had positive HCV RNA with a prevalence of 68.4% (5). Compared with controls; history of blood transfusions, surgery and use of non-disposable syringes was significantly more common among the patients who had positive HCV antibody (blood transfusion: $p < 0.05$, surgery: $p < 0.01$ and the use of non-disposable syringes, $p < 0.005$) (5). A study from Japan revealed 8.8% and 13.1% of HCV antibody seropositivity in hospital and autopsy cases older than 60 years of age, respectively (6).

Brind *et al* (7) studied HCV infection in 25 patients who were older than 65 years of age. HCV RNA was detected in 95% of patients. The identifiable potential risk factors for HCV infection were history of blood transfusion, war service, tattoos, hemodialysis and being a health care worker (7). In this study, HCV genotype 1b was the most prevalent involving 63% of elderly patients with HCV (7).

In a large Italian study that was conducted among 1646 subjects, the prevalence of positive HCV antibody was reported as 5% in patients age 58 to 67 years old and 2% in patients age 68 and 77 years old (8).

NATURAL HISTORY

According to an Italian study that included 392 patients with a known history of single blood transfusion in the past, the time from the age at purported infection (blood transfusion) to the development of cirrhosis was shorter if the infection was acquired at an older age (9). The age at the time of infection was significantly associated with the development of cirrhosis at multivariate analysis ($p = 0.001$) (9). The median time from the age of infection to the onset of cirrhosis that was 33 years in patients who acquired the HCV infection at the age of 21 to 30 was reported to decrease to 16 years in patients who had the infection after the age of 40 (9).

Similar results were found by Tong and colleagues who studied the outcome of transfusion associated HCV progression in 103 patients who received blood transfusion before the age of 50 and 28 patients at the age of 50 or after the age of 50, respectively (10). The mean time from the age of blood transfusion to the development of cirrhosis was reported to be 9.8 years in patients who had blood transfusion at the age of 50 or after whereas the mean time from the age of blood transfusion to the development of cirrhosis was reported to be 23.6 years in patients who had blood transfusion before the age of 50 (10). In addition, they reported that mean time from the age of blood transfusion to the development of hepatocellular carcinoma was 14.7 in patients who had blood transfusion at the age of 50 or after and 31.5 years in those who had blood transfusion before the age of 50 (10).

Investigators from Japan reported a significantly shorter interval between the time of blood transfusion and the diagnosis of HCV- associated hepatocellular carcinoma if the blood transfusion was received at an older age (11).

These results suggest that HCV that is acquired by blood transfusion at an older age progresses more rapidly to end stage liver disease compared to HCV that is acquired at a younger age. Liver fibrosis is another important complication of chronic HCV infection. Poynard *et al* (12) assessed the progression of liver fibrosis by Kaplan-Meier method and rate of fibrosis progression by hazard function in 2313 HCV positive patients who were not previously treated for HCV. They reported that the progression to all stages of fibrosis including F1, F2, F3 and F4 was faster in patients who were over 50 years of age (12). Despite the large number of patients enrolled, the study was not a prospective study, but a cross-sectional study (12). The other limitations of this study included the lack of serial liver biopsies in the study participants

and uncertainty about the duration of HCV infection (12). Given the accelerated course of HCV infection in the elderly, the authors recommended that HCV patients should be identified and treated before they reach 50 years of age (12).

The investigators from Japan studied the development of liver cancer in HCV antibody positive patients with chronic liver disease with cirrhosis and without cirrhosis who were 80 years old or older (13). According to this study, the cumulative rates for developing liver cancer continued to increase over 7 years of follow-up in both non-cirrhotic and cirrhotic groups being 11.1% and 37.1% at the end of 7th year, respectively (13).

Patients with chronic HCV can develop hepatocellular carcinoma (HCC) even if they are successfully treated for HCV infection and have a sustained virologic response (SVR) (undetectable serum HCV RNA by PCR for 6 months after stopping the HCV treatment) (14). A study from Japan that investigated the outcome of HCV patients with SVR revealed that 3.5% of these patients developed HCC (14). The patients who developed HCC despite the SVR after HCV treatment were significantly older when they received interferon treatment compared with patients who had SVR and did not have HCC (mean age 58 vs. 49; $p=0.002$) (14). However, this comparison was done with relatively small number of cases (13 patients with SVR who developed HCC) compared to that of controls (360 patients with SVR who did not develop HCC) (14).

Thabut *et al* (15) conducted a retrospective study in 6865 HCV positive patients who were 65 years old or older. The study showed that older age at infection was significantly associated with higher stages of fibrosis (mean age 25.4 vs. 29.8, $p < 0.001$) (15). Authors had made the adjustment for the duration of the HCV infection, a potential confounder in the study (15). This result confirmed the findings of the previous studies (9,10,12,15). In addition, the manifestation of HCV infection in the elderly was in the form of a complication of chronic hepatitis and this was significantly more often compared with younger patients' initial disease manifestation (15).

HCV TREATMENT IN THE ELDERLY

There are few clinical studies conducted in HCV positive elderly patients. One of the major reasons for this could be the exclusion of subjects who were 75 years old or older in HCV related clinical studies (16–18). In several randomized trials, the mean age was reported to be around 40 (19–21). Other reasons for exclusion of older participants could be the increased comorbid conditions at older age, the fear of facing more adverse effects during the HCV treatment or reluctance to perform liver biopsies in the elderly population.

Standard Interferon Treatment in the Elderly with Chronic HCV

In the first three studies below, the response to HCV treatment was defined as normalization of serum alanine aminotransferases (22–24) (Table 1). Others used SVR to determine the efficacy of HCV treatment (25–28).

Bresci *et al* (22) compared the therapy response of HCV patients who were 65 years old or older to that who were younger than 65 (Table 1). Each group received interferon alpha-2b 3 MU three times a week for 6 months (22). There was no statistically significant difference in therapy response rates in each group ($p=0.85$) (22).

According to a study conducted in Japan, the response to interferon monotherapy was 26% in patients who are 60 years or older and not significantly different compared to patients who were younger than 60 (23) (Table 1).

Van Thiel *et al* (24) treated 25 HCV positive patients who were older than 65 with 5MU interferon three times a week for 6 months and compared their treatment response rates with 25 HCV positive patients with a mean age of 44 (Table 1). The therapy response rates were 32% and 28% in the treatment and control group, respectively (24). The authors reported that the severity of the disease did not differ between the groups (24).

Alessi *et al* (28) evaluated the efficacy of HCV treatment by both SVR (Table 1) and long-term response that was defined as undetectable serum HCV RNA during 14 to 82 months of follow-up period (Table 1). Long-term response rates in elderly group was 8% compared to 13% in the younger age group ($p=0.4$) (28).

From a retrospective study from Japan that included 84 patients who were 65 or older, SVR rates were reported as 35.7 % of patients who received IFN monotherapy (29) (Table 1). The major limitation in this study was the lack of a controlled group (29). In addition, the patients were divided into 3 groups and the dose and the duration of therapy were different for each group (29). The drop rate secondary to treatment side effects at the end of 24 weeks was reported as 17.3% (29).

Honda *et al* (26) compared the efficacy of combined interferon plus ribavirin treatment between 66 patients who were 60 years old or older and 154 patients younger than 60 (Table 1). Both groups received interferon alpha-2b 6 to 10 MU once a day for the first 2 weeks, then three times a week for 22 to 46 weeks and ribavirin 600 mg to 800 mg (depending on their weight) once a day for 24 weeks (26). The SVR rates were almost identical in patients who were 60 years old or older and patients younger than 60 being 31.8% and 38.3%, respectively ($p=0.3589$) (26). In addition, the authors compared the SVR rates between patients who were 60 years old or older treated with combined interferon plus ribavirin and 47 historical controls who were at the same age range treated with interferon alpha monotherapy 6 to 10 MU once a day for the first 2 weeks, then three times a week for 22 to 46 weeks (26). The SVR rates were 31.8% and 10.6% in patients who received combination therapy and monotherapy, respectively ($p=0.0084$) (26).

In a prospective study conducted in Japan, patients were treated in 3 separate age groups: < 50, 50–59 and ≥ 60 (27) (Table 1). All groups received interferon alpha-2b 6 to 10 MU once a day for the first 2 weeks, then three times a week for 22 weeks plus ribavirin 600 to 800 mg oral daily depending on the patient's weight (27). The difference in SVR rates of these three groups (50%, 34% and 32% in patients in the age groups of < 50, 50–59 and ≥ 60 , respectively) approached statistical significance ($p=0.078$). However, discontinuation of treatment was significantly more frequent in patients who were 60 years or older compared to patients younger than 60 ($p < 0.001$) (27).

Pegylated Interferon Treatment in the Elderly with Chronic HCV

Floreani *et al* (30) studied the peginterferon plus ribavirin treatment response in 33 HCV positive patients with a mean age of 70.2 and 66 patients with a mean age of 45.2 (control group) (Table 1). Patients were matched by gender, HCV genotype, HCV viral load, grade and fibrosis stage (30). Patients received pegylated interferon alpha-2b 1.5 mcg/kg weekly and ribavirin 10.6 mg/kg daily for 6 to 12 months depending on their genotype (30). SVR rates were significantly lower in the elderly group compared to control group (45.5% vs. 69.7%; $p=0.02$) (30).

A retrospective study from Italy investigated the SVR in 4 different age groups (< 40, 40–49, 50–64 and ≥ 65) (31) (Table 1). Patients were treated with pegylated interferon alpha-2a or 2b plus ribavirin for 6 to 12 months depending on HCV genotype (31). According to multivariate analysis, odds of having SVR was significantly lower in patients who were 40 years old or

older compared to patients who were less than 40 years of age (OR for the age group of 40–49: 0.16; $p=0.006$; OR for the age group of 50–64: 0.13, $p=0.002$; OR for the age group of ≥ 65 : 0.21, $p=0.0037$) (31).

A study from France reported SVR rates in 45% of patients aged 65 or older who were treated with pegylated interferon plus ribavirin treatment (15) (Table 1). According to multivariate analysis, the type of HCV treatment, not the age, was found to be a significant factor in predicting SVR response in the elderly (15). The patients were 5.4 times more likely to achieve SVR with peginterferon and ribavirin combination therapy compared to other treatment modalities including classic interferon, ribavirin, peginterferon monotherapy as well as non pegylated interferon and ribavirin combined therapy (15). HCV treatment discontinuation rates were reported to be 20% in the elderly and this rate was approximately similar to or even lower than the rates reported in several previous HCV studies conducted in younger patients (15, 19,21,32). However, it should be emphasized that HCV treatment in this study was heterogeneous consisting of different types of interferon as well as mono or combined interferon treatment (15). Some studies reported higher therapy discontinuation rates due to adverse effects in the elderly compared to younger patients (20,30).

Another study from France did not show any significant difference in SVR rates between elderly and controlled groups ($P=0.13$) (33) (Table 1). Although the number of patients who had abnormal laboratories that required dose modification was significantly higher in the elderly patient group compared to the controlled group ($P=0.031$), the number of patients who discontinued HCV therapy due to laboratory abnormalities was not significant among the groups (33).

CONCLUSION

Elderly patients with chronic HCV infection have been an understudied population due to several factors. These factors include exclusion of subjects older than 65 years of age in several clinical trials, reluctance to treat HCV infection in the elderly due to fear of dealing with more HCV therapy related adverse effects, comorbidities and risk factors of aging such as decreased glomerular filtration rate that might cause more severe hemolytic anemia with ribavirin and interactions of interferon and ribavirin with several potential geriatric drugs (34–37). Despite these challenges, previous studies showed that HCV treatment was generally well tolerated by the elderly and there was little or no significant difference in SVR as well as therapy discontinuation rates secondary to adverse effects compared to younger age groups. However, there is a need for prospective randomized controlled trials to be conducted in HCV patients older than 65 years of age to better evaluate the safety and efficacy of HCV treatment in this age group. In addition, more epidemiologic studies are needed to better assess the prevalence as well as the risk factors of chronic HCV infection in elderly subjects.

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Comparison Groups															
Comparison Group 1						Comparison Group 2						Comparison Group 3			
Patients with Adverse Events/laboratory abnormalities (%)	Number of Patients	Age	Treatment	SVR (%)	Number of Patients with Side Effects (%)	Number of Patients	Age	Treatment	SVR (%)	Patients with Adverse Events/laboratory abnormalities (%)	Number of Patients	Age	Treatment	SVR (%)	Patients with Adverse Events/laboratory abnormalities (%)
4 [‡]	21	43.3 ± 7.2	IFN alfa-2b SC 3 MU TIW for 6 months	N/A *	0 [‡]	22	71.6 ± 3.9 (mean ± SD)	No treatment	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	25	35–47	IFN alfa-2b SC 5 MU TIW for 6 months	N/A *	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	22	17–59, 44.1 ± 10.5	Recombinant IFN alfa-2a (5 patients), recombinant alfa-2b IFN (3 patients), natural IFN beta (4 patients)	N/A *	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	64	14–59, 47.5 ± 10.2	IFN alfa 3–6 MU TIW for 6–12 months	20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	58	64.1 ± 3.1	No treatment	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Clinical Gastroenterol Hepatol. Author manuscript; available in PMC 2010 October 6.

Comparison Groups															
Comparison Group 1						Comparison Group 2						Comparison Group 3			
Patients with Adverse Events/laboratory abnormalities (%)	Number of Patients	Age	Treatment	SVR (%)	Number of Patients with Side Effects (%)	Number of Patients	Age	Treatment	SVR (%)	Patients with Adverse Events/laboratory abnormalities (%)	Number of Patients	Age	Treatment	SVR (%)	Patients with Adverse Events/laboratory abnormalities (%)
7 [†]	33	50-59, 54.5 ± 2.9	IFN alfa-2b 6-10 MU SQ QD for 2 weeks, then IFN alfa-2b 6-10 MU T1W for 22 weeks and Ribavirin 600-800 mg qD	34	2 [†]	52	< 50, 40.2 ± 6.8	IFN alfa-2b 6-10 MU SQ QD for 2 weeks, then IFN alfa-2b 6-10 MU T1W for 22 weeks and Ribavirin 600-800 mg qD	50	4 [†]	N/A	N/A	N/A	N/A	N/A
17.3 [‡]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2010 October 6.

Comparison Groups											
Comparison Group 1				Comparison Group 2				Comparison Group 3			
Patients with Adverse Events/laboratory abnormalities (%)	Number of Patients	Age	Treatment	SVR (%)	Number of Patients with Side Effects (%)	Number of Patients	Age	Treatment	SVR (%)	Patients with Adverse Events/laboratory abnormalities (%)	Patients with Adverse Events/laboratory abnormalities (%)
21.2 [‡]	54	< 60	IFN alfa-2b 6–10 MU QD for 2 weeks, then IFN alfa-2b 6–10 MU T1W for 22–46 weeks and Ribavirin 600–800 mg qD for 24 weeks	38.3	14.9 [‡]	47 (monotherapy)	≥ 60	IFN alfa-2b 6–10 MU QD for 2 weeks, then IFN alfa-2b 6–10 MU T1W for 22–46 weeks	10.6	8.5 [‡]	N/A
											N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
24.2 [‡]	66	45.2±8.9	PEG-IFN alfa-2b 1.5 mcg/kg QW and Ribavirin 10.6 mg/kg QD for 6–12 months	69.7	12.2 [‡]	N/A	N/A	N/A	N/A	N/A	N/A
0 [‡]	41	50–64	PEG-IFN alfa-2a or alfa-2b + Ribavirin	53.7	0 [‡]	44	40–49	PEG-IFN alfa-2a or alfa-2b + Ribavirin	68.2	4.6 [‡]	38
16.7 [‡]	41	< 60, 44.5 ± 8.7	IFN (1 patient), IFN +ribavirin	51.2	7.3 [‡]	N/A	N/A	N/A	N/A	N/A	N/A

Comparison Groups															
Comparison Group 1					Comparison Group 2					Comparison Group 3					
Patients with Adverse Events/laboratory abnormalities (%)	Number of Patients	Age	Treatment	SVR (%)	Number of Patients with Side Effects (%)	Number of Patients	Age	Treatment	SVR (%)	Patients with Adverse Events/ laboratory abnormalities (%)	Number of Patients	Age	Treatment	SVR (%)	Patients with Adverse Events/laboratory abnormalities (%)
			(27 patients), PEG-IFN+ ribavirin (13 patients) for 24–48 weeks												
Clin Gastroenterol Hepato															