Chronic Hepatitis C Virus Infection in Older Adults

Esther-Lee Marcus1 and Ran Tur-Kaspa2,3

1Acute Geriatric Department, Herzog Hospital, The Hebrew University-Hadassah Medical School, Jerusalem, and 2Department of Medicine D and 3Liver Institute, Rabin Medical Center, Beilinson Campus, Petah Tikva, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Most of the older adults with chronic hepatitis C virus infection acquired the disease earlier in life. These patients often present with complications of liver disease, mainly cirrhosis and hepatocellular carcinoma. The burden of chronic hepatitis C virus infection in elderly persons is expected to increase significantly in the United States during the next 2 decades. It seems important that, for elderly patients with chronic hepatitis C, the risk-benefit of combination antiviral therapy consisting of pegylated interferon and ribavirin should be assessed on an individual basis. Assessment should be performed in all cases before considering treatment, and it should include evaluation of the degree of liver fibrosis by means of liver biopsy or, possibly, by means of noninvasive methods. Novel antiviral drugs that may have fewer adverse effects, such as protease inhibitors, may serve as potential alternatives. It is recommended that elderly patients (up to the age of 75 years) be included in randomized trials of chronic hepatitis C virus infection treatment.

During the past decade, our knowledge of the pathogenesis, clinical course, and treatment of chronic hepatitis C virus (HCV) infection has increased tremendously. Chronic infection is prevalent and may be more severe in the elderly population. It is estimated that physicians will be encountering increasing numbers of elderly persons with liver diseases due to chronic HCV infection. However, there are hardly any data on the various aspects of pathogenesis and treatment of the disease in old age. The aim of this article is to review the data on the epidemiology, immunology, and clinical manifestations of chronic HCV infection in older adults (age, ≥60 years) and to suggest an approach to management of the infection in this population.

EPIDEMIOLOGY

According to the 1999–2002 National Health and Nutrition Examination Survey IV, in the United States, the prevalence of antibodies against HCV (anti-HCV) was 1.6% (241 of 15,079 participants) in the general population aged ≥6 years [1]. The prevalence of seropositivity in this population was lowest among persons aged <29 years (0.4%). The highest rate of infection was observed in the cohort aged 45–49 years (7.1% among men and 2.3% among women). Among persons aged ≥60 years, 1% were anti-HCV positive (G. L. Armstrong, personal communication). Thus, of ~44 million US residents ≥60 years old, ~440,000 might be anti-HCV positive. Most of the current infections were acquired during the 1960s–1980s from exposure to blood or blood products [2]. The rate of new infections decreased sharply in the 1990s with the introduction of anti-HCV blood testing. Nevertheless, the burden of HCV infection is expected to increase as the patients with ongoing long-term infection age and become subject to complications of liver disease, cirrhosis, and hepatocellular carcinoma (HCC) [2–4]. This phenomenon of HCV geroseropidemiology accounts for the estimate that the number of people who have been infected for >20 years could increase 4-fold between 1990 and 2015, from 750,000 to >3,000,000 [4]. The fold increase among persons infected for 30–40 years will be even greater by 2015 [4], and the HCV-related mortality rate will probably double, or even triple, in the next 2 decades [4]. In contrast to the United States, where the highest prevalence is in the cohort of individuals aged 45–49 years, in other countries, such as Japan [5] and Italy [6], the prevalence of HCV infection is low among children and young adults, but it increases at the age of 40 years and continues to increase during aging. In a community-based study in Japan, the prevalence of anti-HCV seropositivity was 3% (1 of 38 persons) in the 20–29-year-old group and increased to 41% (13 of 32) among persons aged 80–89 years [5]. Nursing home residents may represent a pop-
ulation with an increased risk of HCV infection (i.e., a “sicker population” that is more likely to have been exposed to blood transfusion) [7, 8]. A study of a nursing home population (mean age, 79 years) in St. Louis, Missouri, revealed a 4.5% rate of anti-HCV positivity (9 of 199 persons) [7]. HCV RNA was detected in serum samples obtained from 8 residents, only 1 of whom had symptomatic liver disease. On the basis of these findings, it was thus suggested that nursing home residents be screened for anti-HCV antibodies.

**CLINICAL COURSE**

Chronic hepatitis C develops in 55%–85% of individuals infected with HCV [2, 9]. Rates of persistence of HCV infection vary between studies. Among persons infected during childhood or young adulthood, the rate of HCV clearance is probably higher than that among persons infected at an older age [9]. Data from the National Health and Nutrition Examination Survey III (1988–1994) revealed that, among anti-HCV positive subjects aged ≧20 years, there was little variation in age-based prevalence of HCV RNA in serum samples. This prevalence of serum HCV RNA positivity was 2.5-fold higher than that among persons aged <20 years (75.6% vs. 30.1%) [3]. Progressive liver fibrosis and cirrhosis occur in 2%–20% of patients with long-term infection [2, 9]. In cohort studies of patients with chronic HCV infection, the rate of cirrhosis development was higher among those infected at an older age [9]. Meta-analysis of studies showed that, after 20 years, cirrhosis developed in 24% of patients with posttransfusion hepatitis C, compared with only 7% of patients in community-based cohorts (mean age at infection, 42 vs. 29 years) [10]. Among HCV-infected individuals, cirrhosis becomes more prevalent with age. For example, among patients with chronic hepatitis C, the mean age was 39.5 years for those without cirrhosis, 65.4 years for those with cirrhosis, and 70 years for those with HCC [11]. This can be explained by several factors. First, the duration of the infection in older people is longer. Therefore, their liver disease is more severe, and liver cirrhosis and/or HCC have already developed in some. Second, older patients with mild hepatic disease are often asymptomatic, and therefore, they are not referred for evaluation. In patients with HCV infection acquired during transfusion, the median time for development of cirrhosis decreases as the age of infection onset increases [12, 13]. The median time to development of cirrhosis was reported to decrease from 33 years for persons aged 21–30 years at the time of infection to 16 years for persons aged ≧40 years [12].

It is estimated that, each year, HCC will develop in 1%–2% of patients with chronic HCV infection and cirrhosis [2]. The risk of HCC increases significantly with age, probably owing to age-related changes in the ability to repair DNA [14] and to the prolonged interval from the time of infection. The interval between infection and diagnosis of HCC may be shorter when the infection is acquired at an older age [13, 15]. In patients with posttransfusion hepatitis C, the mean time from transfusion to development of HCC was 14.7 years among persons aged ≧50 years at the time of the transfusion (mean age, 58.5 years), compared with 31.5 years among those infected at <50 years of age (mean age, 29.2 years) [13]. Screening for HCC by liver ultrasonography and α-fetoprotein determination every 6 months is recommended for all patients with chronic HCV infection and cirrhosis, unless they have a limited life expectancy or contraindications to HCC treatments [15–17]. Elsewhere, it was suggested that surveillance for HCC in patients ≧70 years of age with chronic HCV infection and cirrhosis improved survival [17].

Poynard et al. [18] examined possible risk factors for liver fibrosis progression in patients with chronic hepatitis C who were referred to liver clinics and found large differences in the rates of fibrosis progression, according to age at the time of infection. For persons <20 years old at the time of infection, there was very slow progression during the subsequent 10 years, whereas for those aged >50 years, fibrosis progression was rapid. The limitation of their study is that it was cross-sectional rather than longitudinal. In addition, their findings may reflect, at least in part, a bias in the selection of patients referred for evaluation.

The mechanisms underlying the relatively rapid progression of liver disease in older adults are not known. Possible mechanisms for the role of aging in fibrosis progression are higher vulnerability to environmental factors (especially oxidative stress), reduction in the rate of hepatic blood flow, and reduced mitochondrial capacity [18]. Higher prevalence of genotype 1 among elderly persons [19, 20], as well as impaired immunity, may explain the significantly higher viremic load in older patients [20].

For patients who have undergone liver transplantation for hepatitis C, donor age rather than recipient age has a major influence on rate of liver fibrosis after transplantation [21, 22]. This supports the reasoning that age-related changes in liver response might be a key factor that determines the increased susceptibility of the older liver to fibrosis. It is noteworthy that the fibrotic reaction to carbon tetrachloride was greater in older than in younger rats [23].

A study in France comparing chronic HCV infection in patients ≧65 years of age with that in younger patients demonstrated that the older group had a significantly longer duration of infection (26 vs. 20 years), a higher age at infection (50 vs. 24 years), higher rates of genotype 1 infection (78% [687 of 881 persons] vs. 57% [1882 of 3301]), and increased likelihood of a history of transfusion (51% [449 of 881] vs. 29% [957 of 3301]) [24]. Among persons who underwent liver biopsy, the fibrosis stage was higher for those aged ≧65 years,
regardless of infection duration. The initial manifestation of infection was more often a complication (jaundice, bleeding, ascites, and HCC) in persons aged ≥65 years than in persons aged <65 years (14% [123 of 881 persons] vs. 4% [132 of 3301 persons]).

A different message derives from a population-based study in Italy of adults aged ≥60 years [25]. Although 4.1% of the participants (44 of 1063) had HCV antibodies, only 54.3% (19 of 35 anti-HCV–positive persons studied) had HCV viremia, all of whom were either asymptomatic or had mild liver disease. The discrepancy between these studies may be due to the differing characteristics of the study populations. The first population consisted only of patients referred for treatment, whereas the second was community based and included all individuals with HCV antibodies. It may well be that many older patients had either recovered from the disease or were asymptomatic carriers.

A National Heart, Lung, and Blood Institute collaborative study followed up patients for ~25 years with posttransfusion hepatitis C (mean age at transfusion, 49 years) and compared them with a group of matched patients without hepatitis C who had undergone transfusion [26]. All-cause mortality was similar in the 2 groups (67% [149 of 222 persons] and 65% [245 of 377 persons], respectively). There was, however, a difference in liver-related mortality, although the overall mortality rate from liver disease was quite low (4.1% [9 of 222 persons] and 1.3% [5 of 337 persons], respectively).

Recently, attention has been directed to other symptoms associated with chronic HCV infection. Up to 30% of patients had psychological disorders, including depression, and up to 67% complained of fatigue [2, 27, 28]. These symptoms may appear even in the absence of clinically significant liver disease. Age of ≥50 years was found to be associated with fatigue [28]. Chronic HCV infection was associated with cognitive impairment, which was reported in patients aged 28–69 years with mild liver disease [29]. The prevalence of cognitive impairment among older patients, who may have a higher susceptibility to this complication, has not been studied. Because depression, fatigue, and cognitive impairment are common among the general elderly population, they may be overlooked in those with HCV infection or may not be attributed to the disease. It has not yet been established whether these symptoms warrant antiviral therapy.

IMMUNOLOGICAL ASPECTS

The immune system plays a role in at least some of the mechanisms underlying the chronic pattern of HCV infection [30]. However, the specific immunological aspects of HCV in aging have hardly been investigated.

HCV persistence and chronic infection in elderly persons may have its roots already at younger age, and therefore, mechanisms underlying the original primary infection are not directly associated with aging. Yet, when primary infection does occur in old age, it may be confronted with a reduction in both innate and induced specific immunologic responses [31], along with the accompanying emergence of new viral variants, as observed in young persons [30].

In persons with chronic HCV infection, both CD4+ and CD8+ T cell functions are affected [30]. It is thus important to note that, with aging, immunity to viral infections is affected by a decrease in T cell function [31], reduced availability of naive cells potentially active to new incognate antigens, and a shift of T cell subsets from naive to activated and/or memory types.

Additionally, repeated antigenic challenges to CD8+ T cells may lead to ultimate anergy, rather than to effective memory [32]. Anergy was causally attributed to chronic T cell divisions, resulting in decreased telomere length and loss of CD28 gene expression, a marker that acts as an essential membrane molecule for T cell triggering [32].

Alterations in the cytokine profile that occur during aging may also affect the course of chronic liver disease in elderly persons [33]. This includes a decrease in IL-2 levels and the shift from a Th1 to a Th2 cytokine response. The elevation in proinflammatory cytokine levels during aging, particularly IL-6 [34], may affect the severity of liver inflammation.

Consequently, the status of the immune system may have an impact on both persistent infection and chronic disease in elderly persons. HCV-infected elderly individuals may thus experience consequences associated with the inefficiency of both the primary response and T cell memory function. Continuous emergence of new viral variants would worsen the situation.

SCREENING ASSESSMENT AND TREATMENT

According to the 2004 guideline of the American Association for the Study of Liver Diseases (AASLD), persons who received transfusion of blood or blood products before July 1992 should be checked for HCV infection [16]. The current standard of care for HCV infection is pegylated IFN-α and oral ribavirin [16, 35]. The goal of antiviral treatment is to prevent complications of the disease, mainly cirrhosis and HCC. We propose that, for all older patients, treatment decisions should be individualized on the basis of the severity of the liver disease, potential for serious adverse effects, likelihood of treatment response, and presence of comorbid conditions. Therapy is contraindicated for patients with decreased life expectancy due to severe hypertension, heart failure, or coronary artery disease; poorly controlled diabetes; or obstructive lung disease [16]. Chest radiography and electrocardiography are prudent to exclude significant pulmonary and cardiac disease that may be exacerbated by ribavirin-associated anemia [36]. We believe that, owing to the higher risk of adverse effects from antiviral treatment for elderly persons, the degree of liver fibrosis should be assessed before consideration of therapy.
The gold standard for assessment of liver fibrosis and inflammation is liver biopsy. However, some physicians are reluctant to perform liver biopsy for elderly patients because of probable increased risk for complications. In an effort to investigate noninvasive methods for assessment of liver fibrosis and inflammation as possible alternatives for liver biopsy, various combinations of serum markers have been studied [37–40]. One panel of serum markers, the FibroTest-ActiTest (Biopredictive) [37], combines the quantitative results of 6 serum markers—levels of a2-macroglobulin, haptoglobin, γ-glutamyl transpeptidase, total bilirubin, apolipoprotein A1, and alanine aminotransferase—together with age (the higher the age, the greater the score [38]) and sex, and using an algorithm, it generates a measure of fibrosis stage and necroinflammatory activity grade. The FibroTest-ActiTest panel thus provides a quantitative estimate of liver fibrosis and inflammation, ranging from 0.00 to 1.00, that corresponds to the Metavir scoring system of fibrosis stages F0–F4 (in which F4 is considered to be cirrhosis, and F2 and F3 are considered to be advanced fibrosis) and necroinflammatory activity grades A0–A3 (in which A0 is considered to be no activity, and A3 is considered to be severe activity) [41]. Another panel of serum markers, FibroSpect II (Prometheus) [39], uses the combination of hyaluronic acid concentration, levels of tissue inhibitors of metalloproteinases, and a2-macroglobulin level. Studies examining the validity of the FibroTest-ActiTest versus that of liver biopsy for patients with chronic hepatitis C did not include elderly patients [40]. In a study of patients with chronic hepatitis C, the prevalence of severe fibrosis estimated by FibroTest-ActiTest was 73% (1121 of 1529) among patients aged ≥65 years, compared with 35% (2419 of 7011) among younger patients [24]. However, because liver biopsy was not documented, it is not clear whether the sensitivity and specificity of the FibroTest-ActiTest are similar for older and younger patients. Note that, despite the higher rate of fibrosis and necrosis among patients aged ≥65 years, the prevalence of elevated alanine aminotransferase levels was similar to that among younger patients [24]. Serum alanine aminotransferase levels in patients aged ≥50 years with liver biopsy–confirmed severe chronic hepatitis C were lower than those in younger patients with the same degree of liver inflammation, according to liver biopsy [42]. This should be taken into account when using serum alanine aminotransferase levels to evaluate the degree of liver inflammation in older adults.

Another method for assessing fibrosis is transient elastography (FibroScan; Echosens), which measures liver stiffness through pulse-echo ultrasonography [38]. In patients with chronic hepatitis C (mean age, 51 years), results of a combination of FibroScan and FibroTest-ActiTest had a high level of agreement with results of liver biopsy [38].

Further evaluation of these methods in studies that include patients aged ≥65 years is needed. These tests may provide an alternative to liver biopsy for some patients with chronic HCV infection.

Regarding treatment, only patients who have liver involvement more severe than portal fibrosis, with at least moderate inflammation and necrosis, and a significant risk of liver cirrhosis during their estimated life expectancy should be considered candidates for therapy. Current recommendations for treatment are based on large, multicenter, randomized, controlled studies [43, 44]. However, these studies excluded patients >65 years of age [45]. They also excluded patients with diseases common in elderly persons, such as renal, coronary, or cerebral vascular diseases; dementia; depression; and anemia or decompensated liver disease. Therefore, there is a problem in applying the results of clinical trials performed thus far to older adults.

There are only a few, nonrandomized studies on treatment of HCV infection in older patients. Early reports did not assess the rate of sustained virologic response [19, 46]. The later case series that did so used regimens that used to be more common, such as IFN monotherapy [47–49] or IFN with amantadine [47]. The rate of sustained virologic response (define as the absence of serum HCV RNA at the end and 6 months after the end of treatment) for patients aged >60 years (mean age, 64 years) was similar to that for younger patients (mean age, 48 years; 18% [9 of 50] vs. 20% [21 of 104]) [48]. Nonrandomized studies showed that IFN monotherapy reduced liver-related mortality among patients aged >60 years of age (mean age, 63 years) with chronic hepatitis C [49] and that patients (median age, 57 years) with cirrhotic hepatitis C treated with IFN had a reduced risk of HCC and an improved survival rate, compared with patients who received no treatment [50].

The efficacy of therapy with IFN (or pegylated IFN) and ribavirin in older adults was reported in 2 small case series. Among 20 patients >65 years of age, the rate of sustained virologic response was 45% (9 patients) [24], and among 30 patients with a mean age of 65 years, 30% (9 patients) achieved a sustained response [51]. The rate of sustained virologic response reported for younger populations treated with pegylated IFN and ribavirin is, on average, 55% [43, 44].

In large, multicenter, randomized trials of therapy with pegylated IFN and ribavirin involving cohorts with a mean age of 42–43 years, older age was associated with poorer response to treatment [43, 44]. On multivariate analysis, age of ≥40 years was an independent predictor of poor response (OR for sustained response of those aged ≤40 years, 2.60) [44]. It is not known whether the rate of response in persons ≥65 years of age is the same as or worse than that for persons 40–65 years of age. Nevertheless, the AASLD guideline does not stipulate an upper age limit for antiviral therapy [16], although, in practice, elderly patients are less considered and referred for treat-
ment. We believe that therapy should be considered for patients up to the age of 75 years (in the United States, among persons aged 75 years, men and women have an average life expectancy of 10.3 and 12.4 years, respectively [52]).

Although a study involving healthy volunteers aged 20–80 years revealed similar pharmacokinetics of pegylated IFN-α2b in all age groups [53], another study found that absorption of pegylated IFN-α2a was delayed and that its half-life was longer in elderly persons [54]. However, there seems to be no need for dose modification for older adults. Because pegylated IFN is not dependent on extensive oxidative metabolism, it is not subject to the inductive or inhibitory activity of other agents. Pegylated IFNα-2a is, however, a mild inhibitor of cytochrome P450 1A2, the enzyme responsible for metabolism of several drugs, such as theophylline, risperidone, clozapine, and tricyclic antidepressants [55].

The prevalence of adverse effects due to IFN therapy, especially lethargy, confusion, and changes in behavior, may be higher for older patients [56]. In a study of patients (mean age, 48.3 years) with chronic hepatitis C treated with IFN, the only risk factor for depression was advanced age [57].

Because a substantial amount of the ribavirin dose is excreted by the kidney, the risk of toxic reactions to this drug may be greater for patients with impaired renal function [36]. Ribavirin should not be administered to patients with a creatinine clearance of <50 mL/min. Ribavirin should be administered to elderly patients cautiously, starting at the lower end of the dosage range, with renal function monitored and dosage adjustments made accordingly. Note that, in this population, the serum creatinine level might remain normal as the glomerular filtration rate decreases. Therefore, estimation of creatinine clearance should be done using equations incorporating age as a variable, such as the Cockcroft-Gault equation [58]. A common adverse effect of ribavirin is reversible hemolytic anemia. Dose reduction is recommended when the hemoglobin level is <10 g/dL, and therapy cessation is recommended when the hemoglobin concentration decreases to <8.5 g/dL [36]. The risk of hemolytic anemia increases with age [59, 60]. The percentage of patients requiring ribavirin dose reduction was 38% (18 of 48) for those ≥55 years old and 21% (16 of 75) for those <55 years old [59].

Virmidine, a liver-targeting prodrug of ribavirin, may be safer than ribavirin [35]. The combination of pegylated IFN and virmidine therapy in a recent randomized, controlled study involving patients with a median age of 49 years (range, 23–68 years) had the same efficacy as pegylated IFN and ribavirin therapy, but the incidence of anemia (hemoglobin level, <10 g/dL) was 4% (5 of 135 patients) in the study group and 27% (12 of 45 patients) in the comparison group [61]. Further investigation is required to assess efficacy of virmidine in older adults; treatment with virmidine may be an alternative to ribavirin therapy, especially for persons with anemia. Novel antiviral drugs, such as protease inhibitors [35], that may have fewer adverse effects may serve as potential alternatives. Importantly, despite the adverse effects of treatment with pegylated IFN and ribavirin, adherence to the therapy (defined as consumption of ≥80% of the dose ≥80% of the time) is crucial to achieve a virologic response [62]. Adherence to the treatment regimen among patients aged ≥56 years was less than that among younger patients [62].

The possibility of an immunotherapeutic approach for treatment of HCV has been raised, on the basis of studies of the trimera murine model [63]. The data point to possible clinical applications of monoclonal antibodies for prevention of primary infection in transplanted livers [63]. It may be worthwhile to investigate the possibility of treatment of HCV-infected elderly persons by combining immunotherapy with decreased doses of drugs, thus reducing the risk of adverse effects.

CONCLUDING REMARKS

Despite the decrease in the incidence of acute hepatitis C, the prevalence of long-standing chronic hepatitis C infection is increasing among older adults. The management of chronic HCV infection in older adults is complex in terms of comorbidities and quality of life.

There are few data on the efficacy of antiviral therapy for elderly persons. Therefore, we recommend that patients up to the age of 75 years be included in trials of chronic hepatitis C treatment.

For elderly patients with chronic hepatitis C, risk-benefit of antiviral therapy should be assessed on an individual basis. There is a need for research on treatments with efficacy that is at least the same as that of pegylated IFN and ribavirin but with fewer adverse effects. Protease inhibitors, as well as immunotherapy, may be possible treatment modalities.

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