Antiviral Therapy in Elderly Patients With Hepatitis C Virus Infection

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Abstract: The emergence of direct-acting antiviral (DAA) agents has revolutionized the treatment schema for hepatitis C virus (HCV) infection. From cure rates to tolerability, DAA agents have shown outstanding profiles compared with the prior therapy of pegylated interferon with ribavirin. However, the efficacy and safety profiles of DAA therapy in older patients, particularly the elderly, have been unclear, and patients in the 1945 to 1965 birth cohort constitute the largest proportion of the HCV population in the United States. Treating elderly patients with pegylated interferon and ribavirin has been challenging due to the frequent presence of multiple comorbidities in the elderly and high discontinuation rates caused by adverse events. Now, as more DAA agents have become widely studied and approved, subgroup analyses for the elderly population are being elucidated. Analysis of the current literature shows that these agents have been effective, well tolerated, and safe in the elderly population. This article highlights the efficacy and safety differences in interferon-based therapy and interferon-free regimens for elderly patients with HCV infection.

Keywords
Hepatitis C virus, elderly, epidemiology, direct-acting antiviral agents, sustained viral response

Rates of hepatitis C virus (HCV) infection are disproportionately higher in older patients. In fact, patients born between 1945 and 1965 represent the highest proportion (70%) of HCV-infected individuals in the United States,[1] and the prevalence of this birth cohort is estimated to be 3.5% according to the US National Health and Nutrition Examination Survey data.[2] Compared with the younger population, the elderly population is more likely to be infected with HCV, with risk factors including male gender, non-Hispanic ethnicity, nonblack race, advanced age, and a history of blood transfusion before 1992.[1] Some studies have defined elderly patients as those greater than 60 years of age, while other studies have used 65 years of age as the cutoff.[1,3-6] Natural history models predict that the prevalence of HCV infection and its complications will increase through the next decade and will mostly affect people greater than 60 years of age.[7]

Table 1. Currently Available Classes of Direct-Acting Antiviral Agents for Treatment of HCV Genotype 1 Infection[a]

Class of Drug	Agent(s)
Protease inhibitor	Simeprevir, paritaprevir
NS5 polymerase inhibitor Nucleotide analogue Nonnucleoside analogue	 Sofosbuvir Dasabuvir
NS5A inhibitor	Ledipasvir, ombitasvir

[a] The combinations currently approved are sofosbuvir plus ledipasvir, sofosbuvir plus simeprevir, and paritaprevir (enhanced with ritonavir) plus ombitasvir plus dasabuvir.

HCV, hepatitis C virus.

Achieving a sustained viral response (SVR) is associated with decreased liver-related complications and overall mortality in patients with advanced liver disease.[8] Elderly patients are more likely than younger patients to have advanced liver disease (likely related concomitant liver conditions), increased duration of infection, and an increased rate of disease progression.[9-12] Due to the increasing risk of cirrhosis[13-15] and hepatocellular carcinoma development[16,17] with advanced age, elderly patients are in special need of an effective antiviral treatment.

The standard of HCV therapy over the past decade has been pegylated interferon and ribavirin. However, many large clinical trials have excluded patients greater than 65 years of age, while other trials have reported high rates of discontinuation in elderly subgroups.[18-21] Widespread use of pegylated interferon/ribavirin in clinical practice among elderly patients has been limited by the inherent adverse effects associated with this approach.[22,23] Comorbidities such as coronary heart disease and diabetes are unfavorable factors for treatment response with pegylated interferon/ribavirin.[20,24] In addition, adverse events and poor tolerability increase with age in pegylated interferon/ribavirin recipients.[21] Thus, elderly patients as well as their physicians are often hesitant to initiate treatment with these agents.[22,23,25]

The availability of noninterferon, direct-acting antiviral (DAA) agents (Table 1) represents a major paradigm shift in the treatment of HCV infection.[3,26,27] These therapies have been shown to achieve higher cure rates and improved side effect profiles in clinical trials. However, due to distinct characteristics of natural history as well as the presence of adverse events and comorbidities, antiviral treatment in elderly patients with HCV will continue to be challenging.

Interferon-Based Therapy

The combination of pegylated interferon and ribavirin has been the standard treatment for HCV infection. However, studies in elderly patients have been limited in comparison with those in the younger population.[28,29] The impact of age in predicting SVR is debatable, but most studies suggest that SVR rates are lower among elderly patients infected with HCV genotype 1 who are treated with interferon-based therapy.[30-42] For genotypes 2 and 3, the SVR rates have been similar regardless of whether the patients are elderly.[30-33]

The relatively low SVR rates in elderly patients are mainly caused by higher rates of virologic nonresponse to dual therapy.[33-35] Higher rates of adverse effects, such as hemolytic anemia, have been seen in elderly patients.[34,43-46] In addition, more concomitant comorbidities have been observed in elderly patients, particularly metabolic (P<.001)[33] and cardiovascular (P<.001)[33] disease, along with renal, pulmonary, and hematologic conditions that prevent the use of interferon and ribavirin.[47] Dose modifications during HCV therapy are made more commonly in elderly than in younger patients.[33,34,36] In multivariate regression analyses, advanced age was an independent risk factor for SVR rates.[31,33,35,41,42] Elderly HCV patients have different clinical characteristics and treatment outcomes from younger patients and, thus, require special attention from their health care practitioners.

Protease Inhibitors

The addition of the first DAA agents, boceprevir (Victrelis, Merck) and telaprevir (Incivek, Vertex), to pegylated interferon/ribavirin combination therapy was associated with higher SVR rates than the pegylated interferon/ribavirin regimen alone, but with more adverse effects. In fact, the manufacturing of telaprevir has been discontinued. There are very limited data on the stratification of SVR according to age in the United States. However, studies from Japan have shown similar SVR rates (69%-85.7%) in elderly patients who are infected with HCV genotype 1 compared with younger patients (82%-90.4%).[48-50]

Adverse effects are more common in elderly patients than in younger patients using telaprevir and boceprevir. For instance, severe anemia, rash, and a rise in creatinine level occur more frequently, leading to significantly greater rates of treatment discontinuation (33% in elderly patients vs 16% in young adults; P=.008).[49]

Polymerase Inhibitors

Although the SVR rates were not explicitly stratified between elderly and nonelderly patients treated with the combination of pegylated interferon/ribavirin and sofosbuvir (Sovaldi, Gilead), Lawitz and colleagues reported that the SVR rates were similar in patients 50 years of age and older (88%) and in patients less than 50 years of age (95%).[3] In addition, according to the prescribing information for sofosbuvir, the SVR rates in patients greater than 65 years of age (n=90) have been similar to the SVR rates in younger patients.[51]

Table 2. SVR Rates Using DAA Agents to Treat HCV Genotype 1 Infection in Elderly Patients

Regimen	Cohort	SVR of Elderly Patients (≥65 y) (n/N, Duration of Therapy)
Sofosbuvir/ledipasvir (without ribavirin)[5]	Genotype 1, treatment-naive	89% (17/19, 8 weeks)
		100% (32/32, 12 weeks)
	Genotype 1, treatment-experienced	100% (8/8, 12 weeks)
3D (with ribavirin)[6]	Genotype 1a, treatment-naive	96% (22/23, 12 weeks)
	Genotype 1a, treatment-experienced	88% (7/8, 12 weeks)
	Genotype 1b, treatment-naive	100% (20/20, 12 weeks)
	Genotype 1b, treatment-experienced	93% (25/27, 12 weeks)

3D, paritaprevir (enhanced with ritonavir) plus ombitasvir plus dasabuvir; DAA, direct-acting antiviral; HCV, hepatitis C virus; n/N, sample size/population size; SVR, sustained viral response.

Interferon-Free Therapy

The sofosbuvir/ribavirin combination achieves high SVR rates in elderly patients. In a phase 3, open-label trial with 34 elderly subjects (age ≥65 years; 22% of 153 Japanese patients with HCV genotype 2), SVR was achieved in 96.7% of overall patients and 94.1% of elderly patients.[52] Treatment-naive and treatment-experienced elderly subjects had SVR rates of 93.3% (14/15) and 94.7% (18/19), respectively. For subjects less than 65 years of age, SVR rates in treatment-naive and treatment-experienced arms were 98.7% (74/75) and 95.5% (42/44), respectively. A greater but not significantly higher incidence of adverse events was observed in elderly compared with younger subjects (76% and 72%, respectively), and the discontinuation rate was 0% in both groups. Elderly patients reported pruritus and anemia as the most common adverse events during treatment.

In the large multicenter trials with sofosbuvir/ribavirin, namely VALENCE, FUSION, FISSION, and POSITRON, subgroup analysis of SVR used age 50 years as the cutoff value, so conclusions on elderly patients cannot be drawn from these studies.[3,26,27] Retrospective analysis of elderly patients from these studies may provide further support in treating HCV genotype 2 infection in elderly patients with sofosbuvir/ribavirin.

Data on treatment with sofosbuvir plus simeprevir (Olysio, Janssen) in elderly patients are limited. In the COSMOS trial, 8 out of 9 subjects age 65 years or older achieved SVR (88.8%). Stratification of adverse events was not performed according to age.[53]

Ledipasvir/sofosbuvir (Harvoni, Gilead) treatment has very promising SVR rates in elderly patients age 65 years and older (Table 2). Recently, Jacobson and colleagues reported a retrospective post hoc analysis of data in elderly patients (n=152) with genotype 1 HCV infection from 3 large phase 3 clinical trials: ION-1, ION-2, and ION-3.[4,5,54,55] The SVR rates with ledipasvir/sofosbuvir combination therapy without ribavirin in elderly patients were 89% (17/19), 100% (40/40), and 97% (30/31) in 8-week, 12-week, and 24-week treatment periods, respectively; ledipasvir/sofosbuvir with ribavirin in elderly patients yielded SVR8, SVR12, and SVR24 rates of 92% (12/13), 97% (28/29), and 100% (20/20), respectively.

The 3D regimen (Viekira Pak, AbbVie)—which consists of paritaprevir (HCV NS3/4A protease inhibitor with ritonavir), ombitasvir (NS5A inhibitor), and dasabuvir (NS5B RNA polymerase inhibitor) with or without ribavirin—shows high efficacy and a strong safety profile in patients 65 years of age and older (Table 2). Flamm and colleagues presented an integrated safety and efficacy analysis of patients 65 years of age and older who received the 3D regimen.[6,56-61] The SVR rate was 97.1%, including 98% in patients with compensated cirrhosis. The overall SVR rate with 3D with or without ribavirin among elderly patients with HCV genotype 1 in both treatment-naive and pegylated interferon/ribavirin–experienced patients was 97% (121/125). The overall adverse events were similar between the age groups; however, the frequency of adverse events was slightly higher for the older group among patients who received ribavirin compared with those who did not (93.9% vs 87.2%), and the majority of these events were mild to moderate in severity. Ribavirin dose modification occurred more frequently in older patients (16.5%) than in younger patients (7.0%). Discontinuation rates due to adverse events were infrequent and similar in younger (1.0%) and older (0.9%) patients.

Analysis and Future Directions

There are 3 all-oral DAA regimens currently approved by the US Food and Drug Administration for the treatment of chronic HCV infection (Table 3).[62-64] This article highlights the efficacy and safety differences between interferon-based therapy and interferon-free regimens for elderly patients. Although interferon-based therapy reaches relatively high SVR rates in elderly patients, as compared with younger patients, higher adverse event rates in the elderly population with comorbidities can be a large barrier in completing the full course of therapy. In

Table 3. Approved DAA Regimens and Their SVR Rates in the Treatment of HCV Genotype 1 Infection

		SVR (n/N, Duration of Therapy)	
Regimen	**Cohort**	**Noncirrhotic**	**Cirrhotic**
Sofosbuvir/ledipasvir[62]	Genotype 1, treatment-naive	94% (202/215, 8 weeks)[a]	
		96% (208/216, 12 weeks)	94% (32/34, 12 weeks)
	Genotype 1, treatment-experienced	95% (83/87, 12 weeks)	100% (22/22, 24 weeks)
Sofosbuvir/simeprevir[63]	Genotype 1, treatment-naive or -experienced	95% (20/21, 12 weeks)	100% (10/10, 24 weeks)
3D[64]	Genotype 1a, treatment-naive	96% (405/422, 12 weeks + RBV)	95% (53/56, 24 weeks + RBV)
	Genotype 1a, treatment-experienced	96% (166/173, 12 weeks + RBV)	95% (62/65, 12 weeks + RBV)
	Genotype 1b, treatment-naive	100% (209/209, 12 weeks, no RBV)	100% (22/22, 12 weeks + RBV)
	Genotype 1b, treatment-experienced	100% (91/91, 12 weeks, no RBV)	98% (45/46, 12 weeks + RBV)

[a] An 8-week course of sofosbuvir/ledipasvir is approved for HCV treatment in treatment-naive, noncirrhotic patients with a viral load of less than 6 million. In this population, the 8-week course is associated with a SVR of 97% (119/123 patients).

3D, paritaprevir (enhanced with ritonavir) plus ombitasvir plus dasabuvir; DAA, direct-acting antiviral; HCV, hepatitis C virus; n/N, sample size/population size; RBV, ribavirin; SVR, sustained viral response.

contrast, interferon-free regimens, regardless of the combinations, have consistently shown very promising cure rates with relatively low incidences of adverse events in the elderly population. Once regarded as a difficult-to-treat subgroup of HCV patients, the elderly population may have an exciting outlook in HCV therapy.

The SVR differences between nonelderly and elderly patients have diminished with the use of interferon-free DAA agents. There may be a number of reasons to explain lower SVR rates using interferon-based therapy. First, tolerability and thus adherence have been shown to decrease with advanced age.[31-33,35-41] The risk of ribavirin-induced hemolytic anemia has been associated with advancing age.[21,34,43-46] Second, hepatocytes appear to undergo a senescence process that blunts the interferon response.[20,65-67] Specifically, chronic oxidative stress from excessive accumulation of vacuoles, lipofuscin, and lysosomes in the hepatocytes of elderly patients interferes with the cellular interferon response pathway.[65-68]

The results of a recent cost-effectiveness study have demonstrated the pharmacoeconomic advantages of treating HCV infection in elderly patients. Younossi and colleagues recently revealed the beneficial economic impact of treating patients born between 1945 and 1965 with interferon-free regimens.[69] In the model, the interferon-free regimen was assumed to have a 98% SVR rate and cost $1000/day for 12 weeks. The researchers concluded that birth cohort screening and treating these patients without staging was a more cost-effective strategy, with an incremental cost-effectiveness ratio of $32,263 per quality-adjusted life-year (QALY), compared with a risk-based screening strategy. With highly efficacious and well-tolerated interferon-free regimens available, screening of the baby boomer birth cohort is highly cost-effective with great health and economic benefits at the population level.

In another model, Rein and colleagues estimated the clinical burden of HCV infection in Medicare costs as of 2009, and forecasted this burden until 2024 assuming 3 treatment strategies: no treatment, treatment with pegylated interferon/ribavirin and a protease inhibitor, and an all-oral DAA regimen.[70] Of the cumulative 1,823,298 individuals with chronic HCV infection currently in Medicare or predicted to enter by 2024, treatment with pegylated interferon/ribavirin and a protease inhibitor and treatment with an all-oral DAA regimen reduced deaths by 29,720 and 126,163, respectively, and increased undiscounted QALYs by 1,562,119 and 7,692,906, respectively. Based on these significant improvements in terms of mortality and QALYs, treatment, especially with all-oral DAA regimens, could substantially reduce morbidity and mortality from HCV infection. Thus, antiviral therapy with DAA agents in the elderly population is cost-effective while mitigating the health consequences of HCV infection.

Summary

The current US Food and Drug Administration–approved, all-oral DAA regimens represent major advances in the treatment of elderly patients infected with HCV. Although these regimens are similar in their mode of action and efficacy rates, there may be important differences in drug interactions and duration of response that may favor one regimen over another. The elderly population represents a large percentage of HCV patients in the United States. The faster progression of advanced fibrosis and related complications associated with this age group, compared with younger individuals, underscores the need for treatment in this traditionally difficult-to-treat group. With their high efficacy rates and tolerability profiles,

the new DAA agents can be used in elderly patients with HCV infection.

Dr Rheem does not have any relevant conflicts of interest to disclose. Dr Sundaram serves on the speakers bureaus and advisory boards of AbbVie, Janssen, and Gilead, and also serves on the speakers bureau for Salix. Dr Saab serves on the speakers bureaus of and is a consultant for AbbVie, BMS, Gilead, and Janssen.

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the scenario of a person being diagnosed with a disease that is curable, but he cannot be treated because he is "not sick enough" according to his insurance provider. The new diagnosis introduced a stressful element into his home, leading to issues with his spouse, and he and his wife do not understand why he cannot obtain the necessary treatment. He said to me, "I was better off not knowing."

G&H Are you doing anything to try to improve access?

DB Yes. I have been trying to reach out to elected officials and any other influential people who may be able to help fight this battle. I have spoken with individuals at pharmaceutical companies and with medical directors at various insurance companies.

G&H Have you made any progress in enabling better access?

DB The medical directors cannot or will not change their policies. Sometimes a decision for an individual patient may be changed, but the written policy of what is covered is not readily changed. Therefore, the likelihood that a patient will be able to obtain these medications depends on the doctor that he or she is seeing and the insurance provider that he or she has.

G&H Are advocacy groups trying to change the situation?

DB Yes, but these efforts must be done regionally because each payor determines criteria by state. There are no national organizations fighting for access, which is problematic. Many grassroots efforts are ongoing, and some headway is being made here and there, but in many places no headway is being made at all. Therefore, whether or not a patient can access treatment may depend not only on his or her disease status but also on his or her zip code.

Dr Bernstein receives research funding from and is a consultant for AbbVie, BMS, Janssen, Merck, and Gilead. He is also on the speakers bureaus of Merck, Gilead, and AbbVie.

Suggested Reading

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