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Editorial Board Member of *World Journal of Hepatology*, Toshiya Kamiyama, MD, PhD, Assistant Professor, Surgeon, Surgical Oncologist, Department of Gastroenterological Surgery I, Graduate School of Medicine, Hokkaido University, Sapporo 060-8638, Japan

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World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Xiu-Xia Song, Director
World Journal of Hepatology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
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PUBLISHER
Baishideng Publishing Group Inc
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Telephone: +1-925-2238242
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Retrospective Cohort Study

Efficacy and safety of sofosbuvir and ledipasvir in Japanese patients aged 75 years or over with hepatitis C genotype 1

Yoshinori Ozono, Kenji Nagata, Satoru Hasuike, Hisayoshi Iwakiri, Kenichi Nakamura, Mai Tsuchimochi, Yuri Yamada, Yuka Takaishi, Mitsue Sueta, Tadashi Miike, Yoshihiro Tahara, Shojiro Yamamoto, Kotaro Shide, Tomonori Hidaka, Yoko Kubuki, Kazunori Kusumoto, Toshimasa Ochiai, Junya Kato, Naoto Komada, Shuichi Hirono, Kazuo Kuroki, Masafumi Shigehira, Kazuya Shimoda

Yoshinori Ozono, Satoru Hasuike, Hisayoshi Iwakiri, Kenichi Nakamura, Yuri Yamada, Yuka Takaishi, Mitsue Sueta, Tadashi Miike, Yoshihiro Tahara, Shojiro Yamamoto, Kotaro Shide, Tomonori Hidaka, Yoko Kubuki, Kazuya Shimoda, Department of Gastroenterology and Hematology, Faculty of Medicine, University of Miyazaki, Miyazaki 889-1601, Japan

Kenji Nagata, Mai Tsuchimochi, Kazuya Shimoda, Department of Liver Disease, University of Miyazaki Hospital, Miyazaki 889-1601, Japan

Kazunori Kusumoto, Toshimasa Ochiai, Department of Internal Medicine, Koga General Hospital, Miyazaki 880-0041, Japan

Junya Kato, Naoto Komada, Department of Internal Medicine, National Hospital Organization Miyakonojo Medical Center, Miyazaki 885-0014, Japan

Shuichi Hirono, Department of Internal Medicine, Hirono Naika Clinic, Miyazaki 880-0925, Japan

Kazuo Kuroki, Department of Internal Medicine, Kushima Municipal Hospital, Miyazaki 888-0001, Japan

Masafumi Shigehira, Department of Internal Medicine, Shigehira Clinic, Miyazaki 885-0005, Japan

ORCID number: Yoshinori Ozono (0000-0003-4616-5831); Kenji Nagata (0000-0001-7861-6372); Satoru Hasuike (0000-0002-5312-5152); Hisayoshi Iwakiri (0000-0001-5657-735X); Kenichi Nakamura (0000-0002-9665-3940); Mai Tsuchimochi (0000-0002-9856-938X); Yuri Yamada (0000-0001-8249-4283); Yuka Takaishi (0000-0003-1936-8705); Mitsue Sueta (0000-0003-2015-5010); Tadashi Miike (0000-0002-2079-1693); Yoshihiro Tahara (0000-0002-2134-6655); Shojiro Yamamoto (0000-0002-0938-7112); Kotaro Shide (0000-0002-0046-3254); Tomonori Hidaka (0000-0002-7018-3653); Yoko Kubuki (0000-0002-0763-9136); Kazunori Kusumoto (0000-0002-2572-9987); Toshimasa Ochiai (0000-0002-9918-1547); Junya Kato (0000-0002-1037-4511); Naoto Komada (0000-0003-2442-2972);

Shuichi Hirono (0000-0002-7833-5703); Kazuo Kuroki (0000-0001-5496-8779); Masafumi Shigehira (0000-0002-1936-6323); Kazuya Shimoda (0000-0001-9051-6534).

Author contributions: Ozono Y and Nagata K contributed to the study conception and design; Hasuike S, Iwakiri H, Nakamura K, Tsuchimochi M, Yamada Y, Takaishi Y, Sueta M, Miike T, Tahara Y, Yamamoto S, Kusumoto K, Ochiai T, Kato J, Komada N, Hirono S, Kuroki K and Shigehira M contributed to data acquisition; Shide K, Hidaka T, Kubuki Y and Shimoda K contributed to drafting the manuscript and revisions; all authors gave final approval of the version to be published.

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Correspondence to: Dr. Kenji Nagata, MD, PhD, Department of Liver Disease, University of Miyazaki Hospital, 5200 Kihara, Kiyotake, Miyazaki 889-1601, Japan. nagatakj@med.miyazaki-u.ac.jp
Telephone: +81-985-859121
Fax: +81-985-855194

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Abstract

AIM

To evaluate the efficacy and safety of a regimen containing sofosbuvir (SOF) and ledipasvir (LDV) in Japanese patients aged ≥ 75 years with hepatitis C genotype 1.

METHODS

This multicenter, retrospective study consisted of 246 Japanese patients with HCV genotype 1 at nine centers in Miyazaki prefecture in Japan. Demographic, clinical, virological, and adverse effects (AE)-related data obtained during and after SOF/LDV therapy were collected from medical records. These patients were divided into two groups, younger (aged < 75 years) and elderly (aged ≥ 75 years). Virological data and AEs were analyzed by age group.

RESULTS

The sustained virological response (SVR) rates at 12 wk after treatment were 99.2%, 99.4%, and 98.7% in the overall population and in patients aged < 75 and ≥ 75 years, respectively. Common AEs during therapy were headache, pruritus, constipation, and insomnia. These occurred in fewer than 10% of patients, and their incidence was not significantly different between the younger and elderly groups. Two patients discontinued treatment, one due to a skin eruption and the other due to cerebral bleeding.

CONCLUSION

Compared with younger patients, elderly patients had a similar virological response and tolerance to SOF/LDV therapy.

Key words: Chronic hepatitis C; Sofosbuvir; Ledipasvir; Sustained virological response; Direct acting antivirals

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Core tip: Most Japanese patients with hepatitis C are elderly, and those aged ≥ 75 years account for more than 50%. However there are few reports regarding sofosbuvir (SOF) and ledipasvir (LDV) therapy in patients aged ≥ 75 years in the real-world. The present study demonstrated that patients aged ≥ 75 years had a similar virological response and tolerance to SOF/LDV therapy compared with patients aged < 75 years in the real-world cohorts. Therefore, SOF/LDV therapy might be effective and safe in elderly patients.

Ozono Y, Nagata K, Hasuike S, Iwakiri H, Nakamura K, Tsuchimochi M, Yamada Y, Takaishi Y, Sueta M, Miike T, Tahara Y, Yamamoto S, Shide K, Hidaka T, Kubuki Y, Kusumoto K, Ochiai T, Kato J, Komada N, Hirono S, Kuroki K, Shigehira M, Shimoda K. Efficacy and safety of sofosbuvir and ledipasvir in Japanese patients aged 75 years or over with hepatitis C genotype 1. *World J Hepatol* 2017; 9(36): 1340-1345 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i36/1340.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i36.1340>

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the major global causes of liver-related diseases such as chronic hepatitis, liver cirrhosis, liver failure, and hepatocellular carcinoma (HCC)^[1,2]. In Japan, the prevalence of anti-HCV antibodies in the general population was estimated to be 0.9%^[3], and significantly increased with age^[3,4]. In fact, most Japanese patients with hepatitis C are elderly, and those aged ≥ 75 years account for more than 50%^[5]. However, elderly patients (≥ 75 years) treated with interferon-based therapies have poor sustained virological response (SVR) rates and high discontinuation rates due to adverse effects (AEs)^[6]. Moreover, in Japan the proportion of patients with HCV genotype 1 infection was found to 70%; most were reported to be infected with subgenotype 1b, compared to only approximately 1% with subgenotype 1a^[7]. These population was known to exhibit treatment resistance with interferon (IFN) therapy^[8], therefore novel anti-viral therapies for this population are urgently needed.

In 2014, the combination of daclatasvir (DCV), an NS5A inhibitor, and asunaprevir (ASV), an NS3/4A protease inhibitor, was the first interferon-free regimen to be approved for Japanese patients with HCV genotype 1^[9]. Moreover, in 2015, the HCV NS5A inhibitor ledipasvir (LDV) and the HCV polymerase inhibitor sofosbuvir (SOF) were approved for this same population^[10]. These regimens have demonstrated high efficacy with an improved safety profile and shorter treatment duration than interferon-based therapies^[9,10]. However, patients aged ≥ 75 years were excluded from these clinical trials^[9,10], and therefore no data have been reported regarding the efficacy and safety of these regimens in this population. Recently, with respect to DCV/ASV therapy, several real-world studies showed that the SVR rate and discontinuation rate due to AEs were comparable in patients aged ≥ 75 and < 75 years^[11-13]. On the other hand, there are few reports regarding SOF/LDV therapy in patients aged ≥ 75 years. Therefore, in the present study, we assessed the efficacy and safety of SOF/LDV therapy in Japanese patients aged ≥ 75 years with hepatitis C genotype 1.

MATERIALS AND METHODS

Patients and therapy regimens

Between September 2015 and December 2016, 246 patients infected with HCV genotype 1 were treated with SOF/LDV at nine centers in Miyazaki prefecture in Japan. Demographic, clinical, virological and AE-related data obtained during and after therapy were retrospectively collected from medical records. Patients who had already received DCV/ASV therapy were excluded. Cirrhotic patients with Child-Pugh class B and C were excluded. Patients received 12 wk of treatment with a fixed-dose combination tablet containing 90 mg of LDV and 400 mg of SOF, administered orally once daily. In a phase 3 clinical trial in Japan, the addition of ribavirin to SOF/LDV did not improve the SVR12 rate, but did increase the number of AEs^[10]. Thus, the combination of ribavirin and SOF/LDV is not approved in Japan for the treatment of chronic HCV infection, including in cirrhotic or treatment-experienced patients. Patients were divided into younger (< 75 years) and elderly (\geq 75 years) groups, and clinical data were analyzed by group. This study was approved by the Research Ethics Committee of the University of Miyazaki.

Laboratory and virological assessments

Laboratory tests were performed at baseline, at weeks 4, 8, and 12 during therapy, and at 4, 8, and 12 wk after therapy. HCV RNA was measured using the COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). The dynamic range was 1.2–7.8 log IU/mL. HCV RNA levels were measured at weeks 4, 8, and 12 during therapy, and at weeks 4, 8, and 12 after therapy. Liver cirrhosis was diagnosed clinically based on laboratory tests and imaging findings, including portosystemic shunt, splenomegaly, or esophageal/gastric varices. The fibrosis-4 index (Fib-4) was calculated before the initiation of SOF/LDV therapy. NS5A resistance-associated variants (RAVs) (Y93C/H/N/S or L31I/F/M/V) of HCV were tested by direct sequencing in some patients. In this study, virological responses were categorized as follows: Undetectable HCV RNA at 4 wk after the initiation of therapy was defined as rapid virological response (RVR), and that at 12 wk after the end of the therapy was defined as sustained virological response (SVR12). Relapse was defined as undetectable HCV RNA levels by the end of therapy and detectable levels during the follow-up period.

Statistical analysis

Statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, version 20.0). Baseline continuous data are expressed as median, and categorical data are expressed as number and percentage. The effectiveness of SOF/LDV therapy was evaluated using intention-to-treat analysis. Univariate analyses were performed using the χ^2 , Fisher's exact, or

Mann-Whitney *U* tests. *P* values < 0.05 were considered statistically significant in all analyses.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. The median age was 69 years (range, 29–88 years), and 79 (32%) patients were aged \geq 75 years (elderly group). Of the 246 patients, 103 (42%) were male. Fifty-one patients (21%) had cirrhosis, and all were Child-Pugh class A. Sixteen patients (7%) were previously treated for HCC. Fifty-two patients (21%) previously received interferon-based therapy. Of the 75 patients who were tested for HCV NS5A-RAVs before therapy, 22 (29%) were positive at baseline. Of these, only five had both NS5A Y93 and L31. Before therapy, the median HCV viral load was 6.1 log IU/mL (range 1.6–7.3 log IU/mL). Baseline platelet count and glomerular filtration rate were lower and FIB4 was higher in the elderly.

Effectiveness

The overall RVR rate was 86.9%. All patients had undetectable HCV RNA at 8 wk of therapy, and none exhibited viral breakthrough during treatment. The SVR12 rates were 99.2%, 99.4%, and 98.7% in the overall population and in patients aged < 75 and \geq 75 years, respectively. Table 2 shows the SVR12 rates according to various clinical and demographic factors. There was no difference between the two groups in any parameter. Two patients experienced virological relapse, one after 4 wk (elderly patient) and the other after 8 weeks (younger patient), and one of these had an NS5A RAV (L31M) at baseline.

Safety and adverse events

The safety profile for SOF/LDV is shown in Table 3. Common AEs during therapy were headache, pruritus, constipation, and insomnia. All were found in fewer than 10% of patients, at similar rates in the elderly and younger groups. Serious AEs, including hematological and laboratory abnormalities, were rare. None of the patients had decreased hemoglobin levels or platelet counts, and none had elevated total bilirubin levels over 3.0 mg/dL, alanine aminotransferase levels over five times the upper limit of normal, or creatinine levels over 1.5 times baseline values. Two patients (0.8%) discontinued therapy prematurely, one due to cerebral hemorrhage (pontine hemorrhage) at 7 wk after initiation of therapy, and one due to a skin eruption after 10 wk. The former was a 62-year-old man, while the latter was a 72-year-old woman. Both patients were treatment naïve, and eventually achieved SVR12.

DISCUSSION

Recently, a number of oral direct-acting antivirals (DAAs)

Table 1 Baseline characteristics

Characteristics	Total (n = 246)	< 75 yr (n = 167)	≥ 75 yr (n = 79)	P value
Sex (male)	103 (42)	65 (39)	37 (47)	0.239
Age (yr)	69 (29-88)	65 (29-74)	78 (75-88)	< 0.001
Body weight (kg)	53 (35-91)	53 (38-91)	53 (35-78)	0.527
Cirrhosis	51 (21)	30 (18)	21 (26)	0.120
HCV RNA (log ₁₀ IU/mL)	6.1 (1.6-7.3)	6.1 (1.6-7.3)	6.1 (4.0-6.8)	0.337
Hemoglobin (g/dL)	13.6 (9.0-16.8)	13.6 (9.5-16.8)	13.3 (9.0-15.9)	0.163
Platelets (× 10 ⁹ /L)	156 (26-340)	167 (26-340)	132 (57-278)	0.001
Aspartate aminotransaminase (U/L)	42 (17-191)	40 (17-191)	45 (20-155)	0.140
Alanine aminotransaminase (U/L)	38 (11-319)	38 (12-319)	37 (11-167)	0.341
eGFR (mL/min per 1.73 m ²)	72 (36-132)	76 (38-132)	63 (36-98)	< 0.001
α-fetoprotein (ng/mL)	4 (1-382)	4 (1-382)	4 (1-74)	0.525
Fib-4 index	3.3 (0.5-23.2)	2.5 (0.5-23.2)	4.4 (1.5-10.7)	< 0.001
NS5A RAVs				
Y93	22 (29)	10 (21)	12 (43)	0.146
L31	6 (8)	3 (6)	3 (11)	0.798
Y93/L31	5 (7)	4 (9)	1 (4)	0.645
Treatment experienced	52 (21)	41 (25)	11 (14)	0.064
Previous HCC treatment	16 (7)	11 (7)	5 (6)	0.841

Data are expressed as *n* (%) or median (range). eGFR: Estimated glomerular filtration rate; RAVs: Resistance-associated variants; HCC: Hepatocellular carcinoma.

Table 2 Sustained virological response 12 rates according to clinical and demographical factors

Parameters	n	SVR 12 (%)	P value
Sex			0.6272
Male	103	100.0	
Female	143	98.6	
Age (yr)			0.8287
< 75	167	99.4	
≥ 75	79	98.7	
HCV RNA (log ₁₀ IU/mL)			0.7076
< 6.0	93	100.0	
≥ 6.0	153	98.7	
Liver fibrosis			0.8811
No cirrhosis	195	99.5	
Cirrhosis	51	98.0	
Fib-4 index			0.4634
< 3.25	125	100.0	
≥ 3.25	121	98.3	
Prior treatment			0.8931
Treatment naïve	194	99.0	
Treatment experienced	52	100.0	
Previous HCC treatment			0.2868
No	230	99.6	
Yes	16	93.8	
NS5A RAVs			0.5471
None	48	97.9	
Y93	22	100.0	
L31	6	83.3	
Y93/L31	5	100.0	

RAVs: Resistance-associated variants; HCC: Hepatocellular carcinoma; SVR: Sustained virological response.

for HCV treatment were introduced worldwide, and have been reported to be more effective and safer compared with IFN-based therapies. In 2015, the combination of the NS5B polymerase inhibitor SOF and the NS5A inhibitor LDV was approved in Japan^[10]. This regimen have demonstrated high efficacy with an improved safety profile and shorter therapy duration than interferon-

Table 3 Safety profile

	Total (n = 246)	< 75 yr (n = 167)	≥ 75 yr (n = 79)
Common adverse effects			
Headache	6 (2.4)	4 (2.4)	2 (2.5)
Pruritus	2 (0.8)	0	2 (2.5)
Constipation	2 (0.8)	2 (1.2)	0
Stomatitis	2 (0.8)	2 (1.2)	0
Skin eruption	1 (0.4)	1 (0.6)	0
Chill	1 (0.4)	1 (0.6)	0
Nausea	1 (0.4)	1 (0.6)	0
Fever	1 (0.4)	1 (0.6)	0
Insomnia	1 (0.4)	1 (0.6)	0
Hematological abnormalities			
Hemoglobin < 10.0 g/dL	0	0	0
Platelet count < 50 × 10 ⁹ /L	0	0	0
Laboratory abnormalities			
Total bilirubin > 3.0 mg/dL	0	0	0
Alanine aminotransferase > 5 × ULN	0	0	0
Serum creatinine > 1.5 × baseline	0	0	0
Death	0	0	0
Discontinuation due to adverse effects	2 (0.8)	2 (1.2)	0
Cerebral hemorrhage	1 (0.4)	1 (0.6)	0
Skin eruption	1 (0.4)	1 (0.6)	0

Data are expressed as *n* (%).

based therapies, however, patients aged ≥ 75 years were excluded from this clinical trials^[10]. Moreover, the majority of Japanese patients with hepatitis C are elderly, and in particular, those aged ≥ 75 years account for more than 50% of this population^[5]. In our study, patients aged ≥ 75 years showed a high SVR rate (98.7%) and none discontinued treatment due to AEs. Moreover, both the SVR rate and rate of discontinuation secondary to AEs were nearly equal in elderly (≥ 75 years) and younger (< 75 years) patients. Although real-world cohort studies demonstrating the effectiveness of several SOF-containing regimens in elderly patients

have been published worldwide^[14-16], to the best of our knowledge, this is the first real-world study focusing on a high SVR rate and low discontinuation rate due to AEs in Japanese HCV genotype 1 patients aged ≥ 75 years following SOF/LDV therapy.

Elderly patients in the present study were more likely to have advanced liver fibrosis than younger patients because of their lower platelet counts and higher Fib-4 index. This is consistent with a previous report showing that the prevalence of advanced fibrosis was higher in the elderly than in a younger population^[17]. Only 32% of the HCV patients in our sample were over 75 years old, while Karino^[5] found that over 50% of people with HCV in Japan are age 75 years or older, as mentioned above. Elderly patients accounts for the majority of those with advanced cirrhosis (Child-Pugh class B or C), and patients with this condition were excluded from the present analysis. It is suggested that this is the reason for the relatively low proportion of elderly patients (≥ 75 years) compared with younger patients (< 75 years) in our study. Although advanced fibrosis was found to lower the SVR rate achieved by interferon-based therapy in patients with HCV genotype 1^[18], SOF/LDV therapy resulted in similarly high SVR rates in cirrhotic and non-cirrhotic patients, both in a clinical trial^[10] and in the real world^[19-21]. Likewise, in our study the SVR rate was high irrespective of liver status.

Two of 246 patients in our study experienced virological relapse, one of whom had an NS5A RAV (L31M) at baseline. Although pre-existing NS5A and NS5B RAVs for HCV genotype 1b were shown to have a minimal influence on SVR rates following SOF/LDV therapy^[22,23], Ogawa *et al.*^[24] reported that cirrhotic patients with pre-existing NS5A RAVs had significantly lower SVR12 rates than those without these RAVs at baseline. In the present study, one of the two relapsed patients had an NS5A RAV (L31M) and liver cirrhosis, which may have prevented the achievement of SVR12. However, the other had no NS5A RAVs or cirrhosis at baseline, so there were no common factors that were obviously associated with therapy failure.

Our study has several limitations. First, it used a retrospective design. Second, NS5A RAVs could not be tested in all patients and few patients failed to achieve SVR12, therefore we could not correlate NS5A RAVs with therapy failure. Further research including a large number of patients is necessary.

In conclusion, SOF/LDV therapy resulted in similarly high virological response and good tolerance in elderly and younger patients, and may therefore be effective and safe in patients aged ≥ 75 years.

ARTICLE HIGHLIGHTS

Research background

The majority of Japanese patients with hepatitis C are elderly, however, elderly patients (≥ 75 years) treated with interferon (IFN)-based therapies have poor sustained virological response (SVR) rates and high discontinuation rates due to AEs. As a result, it is critical that new anti-viral therapies be developed for

elderly patients. The combination of sofosbuvir (SOF) and ledipasvir (LDV) was approved in Japan, and though this regimen has demonstrated high efficacy with an improved safety profile and shorter therapy duration than IFN-based therapies, there are few real-world studies of Japanese patients aged ≥ 75 years.

Research motivation

Evaluating the efficacy and safety of SOF and LDV in elderly patients with hepatitis C genotype 1 will help clinicians assess whether they can treat these patients similarly to younger patients in the real-world.

Research objectives

To evaluate the efficacy and safety of SOF and LDV in Japanese elderly patients with hepatitis C genotype 1.

Research methods

Demographic, clinical, virological, and AE-related data obtained during and after SOF/LDV therapy were retrospectively collected from medical records.

Research results

The SVR rates at 12 wk after treatment were 99.2%, 99.4%, and 98.7% in the overall population and in patients aged < 75 and ≥ 75 years, respectively. Common AEs occurred in fewer than 10% of patients, and their incidence was not significantly different between the younger and elderly groups.

Research conclusions

The present study demonstrated that patients aged ≥ 75 years had a similar virological response and tolerance to SOF/LDV therapy compared with patients aged < 75 years in a real-world cohort. Therefore, SOF/LDV therapy might be effective and safe in elderly patients.

Research perspectives

Further prospective studies with large sample sizes are necessary.

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