Journal of Clinical Virology. 2017; 88: 58-61

Real life experience with direct-acting antivirals agents against hepatitis C infection in elderly patients

Iria Rodríguez-Osorio[a], Purificación Cid[a], Luis Morano[b], Ángeles Castro[a], Marta Suárez[b], Manuel Delgado[a], Luis Margusino[a], Héctor Meijide[a, c], Berta Pernas[a], Andrés Tabernilla[a], José D. Pedreira[a], Álvaro Mena[a], Eva Poveda[a]

[a] *Grupo de Virología Clínica, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Universidade da Coruña (UDC), Spain*
[b] *Unidad de Patología Infecciosa, Servicio de Medicina Interna, Hospital Álvaro Cunqueiro, Complejo Universitario de Vigo, Spain*
[c] *Servicio de Medicina Interna, Hospital Quirón, A Coruña, Spain*

Abstract
Background. New direct-acting antivirals agents (DAAs) are very safe and well tolerated.
Objectives. The purpose of this study is to analyse the efficacy and safety of DAAs in elderly patients, who have co-morbidities and are on chronic medications.
Study design. All HCV-infected patients over 65 years old in clinical follow-up at two Hospitals in Spain who initiated anti-HCV therapy were included (August 2012–October 2015).
Results. A total of 120 HCV mono-infected patients were recorded. Mean age of patients was 72.6 ± 7.4 years. There were 53.3% women and GT1b was the most frequent (83.3%); 64.2% had cirrhosis and 42.5% were treatment experienced. Ombitasvir + Paritaprevir/r ± Dasabuvir ± Ribavirin (RBV) and sofosbuvir/ledipasvir ± RBV were the most frequently used regimens. Weight-adjusted dosing of RBV was included in 61.7% and 43.6% of them required a dose reduction. Most of the patients (86.7%) had concomitant chronic medication and in 35.8% adjustment was necessary. Adverse events (AE) were seen in 65% of the patients; more frequent when a protease inhibitor (PI) was being used. The sustained virological response (SVR12) per ITT was 88.3%. Only 3 patients discontinued treatment and 2 patients died.
Conclusions. High rates of SVR12 (88.3%) were observed among elderly patients with DAAs-based regimens. The presence of AE was frequent (65%). The majority of these patients (86.7%) had concomitant medication that required adjustment in 1/3 of them. These findings highlight the high rates of response to DAAs in the elderly HCV-population. However, special caution must be taken when using RBV and a PI.

Graphical abstract

High rates of SVR12 (88.3%) were observed among elderly patients with DAAs-based regimens. The majority of these patients (86.7%) had concomitant medication that required adjustment in 1/3 of them. The presence of adverse event was frequent (65%) during HCV treatment, more frequent when a protein inhibitor or ribavirin was part of the regimen. Adverse events and modification of chronic medications make these patients a special population, where we had to exercise more care.

1. Backgorund

Hepatitis C Virus infection (HCV) continues to be a major public health problem affecting 130–150 million people globally [1]. The prevalence of chronic hepatitis C virus (CHC) infection in Spain is estimated around 2.5%–2.9%, and it increases with age [2]; [3]; [4]; [5]. Most studies have consistently found that age and age onset of infection are major factors influencing the degree of fibrosis. In patients over 50-years-old, the rate of progression of fibrosis accelerates, regardless of the duration of infection [6]; [7].

Moreover, age has been a major limitation using pegylated interferon (Peg-IFN) and RBV because its poor tolerability and poorer response in older patients [8]; [9]; [10]. The new DAAs have demonstrated high efficacy, safety and tolerability. Therefore, elderly patients in whom co-morbidities and concomitant chronic medications exist, might benefit from these therapies. However, these patients represented less than 15% in clinical trials and were mainly non-cirrhotic, in contrast with the real life population [11].

2. Objectives

In this context, the purpose of this study is to analyse the efficacy and safety of different anti HCV treatments including DAAs in a real-life cohort of elderly patients.

3. Study design

This is an observational prospective study including all CHC infected patients over 65 years old who received HCV treatment based on DAAs at two hospitals in the Northwest Spain between August 2012 and October 2015.

The study protocol was reviewed and approved by a Medical Ethics Committee and this publication is in accordance with the community standards. All the study participants were informed before the study inclusion.

All demographic, virological, clinical, laboratory, liver fibrosis status, antiviral regimen, the pharmacotherapeutic profile and adherence data were recorded.

The treatment options available for HCV therapies based on DAAs during the study period were: telaprevir(TEL)/boceprevir(BOC)/simeprevir(SIM)/sofosbuvir(SOF) + Peg-IFN + RBV, SOF + RBV, SOF + ledipasvir(LDV) ± RBV, ombitasvir + paritaprevir/ritonavir (2D) ± dasabuvir (3D) ± RBV, SOF + SIM ± RBV and SOF + daclatasvir(DCV) ± RBV. Co-morbidities, chronic medications, HCV status and facilities to an appropriate adherence were taken into consideration for best treatment selection.

The virological endpoint was the achievement of SVR12. Adverse events (AE), changes in chronic medication and adherence were recorded as secondary clinical endpoints.

A descriptive analysis was performed for all variables. Continuous variables were reported using means ± standard deviations or median (range), as indicated. For dichotomous/categorical variables, absolute numbers and percentages were computed. The comparison of quantitative parameters was carried out using Student's t/Mann-Whitney test, as appropriate. The association of qualitative variables was carried out using Chi-squared statistic. An intention to treat analysis (ITT) was done, to evaluate SVR12. Statistical analysis was performed using SPSS for Windows (version 19.0, SPSS Inc., Chicago, Illinois).

4. Results

A total of 120 CHC monoinfected patients were included. Main demographic and virological characteristics are described in Table 1. Mean age of patients was 72.6 ± 7.4 years, there were 53.3% women, 100% were caucasian and GT1b was the most frequent (83.3%). 64.2% had cirrhosis.

Table 1. Demographic and virological characteristics of the study population.

	n=120
Gender, % (n)	
Men	46.7 (56)
Women	53.3 (64)
Age, years old; mean ± SD	72.6 ± 7.4
>80 years old, % (n)	10.8 (13)
Genotype, %(n)	
1a	5.8 (7)
1b	83.3 (100)
1, unknown subtype	6.7 (8)
2	2.5 (3)
3	0.8 (1)
4	0.8 (1)
HCV RNA viral load, log UI/mL; median (range)	6.08 (4.09−7.9)
Fibrosis stage, % (n)	
F0-F1	4.2 (5)
F2	10.8 (13)
F3	20.8 (25)
F4	64.2 (77)
Child Pugh Score, % (n)	
A	95.0 (71)
B	5.0 (6)
Fibrosis measured by Fibroscan, kPa; median (range)	17.4 (1.1–48.0)
Previous exposure to treatment, % (n)	
Naive	57.5 (69)
Relapser	11.7 (14)
Partial responder	6.7 (8)
Null responder	16.7 (20)
Unknown response	7.5 (9)

The specific treatment combinations and the AE related to the study medication are depicted in Table 2. Briefly, 3D/2D ± RBV and SOF/LDV ± RBV were the most frequently used regimens. The duration of HCV treatment was in the majority of the cases (82.6%) 12 weeks.

Table 2. HCV regimens used in the study population.

HCV regimens used in the study population	n = 120 (%)
Ombitasvir + Paritaprevir/r + Dasabuvir + Ribavirin	31 (25.8%)
Ombitasvir + Paritaprevir/r + Dasabuvir	23 (19.2%)
Sofosbuvir + Ledipasvir	19 (15.8%)
Sofosbuvir + Ledipasvir + Ribavirin	13 (10.8%)
Sofosbuvir + Simeprevir + Ribavirin	11 (9.2%)
Telaprevir + Interferon + Ribavirin	7 (5.8%)
Sofosbuvir + Simeprevir	5 (4.2%)
Simeprevir + Interferon + Ribavirin	3 (2.5%)
Sofosbuvir + Ribavirin	3 (2.5%)
Sofosbuvir + Daclatasvir + Ribavirin	2 (1.7%)
Boceprevir + Interferon + Ribavirin	2 (1.7%)
Ombitasvir + Paritaprevir/r + Ribavirin	1 (0.8%)
Adverse events in the study population	n = 120 (%)
Adverse events	78 (65.0%)
Asthenia	47 (39.2%)
Anemia	45 (37.5%)
Pruritus and dried mucosas	20 (16.5%)
Hyperbilirubinemia	14 (11.7%)
Insomnia	4 (3.3%)
Irritability	3 (2.5%)
Liver decompensation	1 (0.8%)
Ascites	
Encephalopaty	

Most patients (69.2%) received a PI based regimen. Many of them had at least one AE compared to those who were not exposed to a PI (74.7% vs. 45.9%; OR: 3.49, CI95%: 1.54–7.84, $p = 0.002$). This association remained significant even after adjustment for the use of RBV: the OR for PI use was 3.10 (CI95%: 1.20–8.00, $p = 0.019$) and for RBV use was 10.17 (CI95%: 4.10–25.23, $p < 0.001$).

Weight-adjusted dosing of RBV was included in 61.7% of regimens and 43.6% of them required a dose reduction. This dose reduction was mostly related to anemia and was performed on week 4 of treatment in the majority of the patients (61.8%).

Two hepatocellular carcinomas (HCC) were diagnosed after the initiation of DAA regimen in two cirrhotic patients, they were following HCC screening program before the initiation of the study medication; one of them with an ultrasound image at the beginning of HCV treatment, with no evidence of tumour.

Most patients (86.7%) had concomitant chronic medication; 77.6% had at least one additional chronic medication. The most frequent chronic medications were antihypertensive (58.3%), proton pump inhibitors (27.5%), benzodiazepines (22.5%), antidiabetic agents (17.5%) and statin (10%). Before the initiation of HCV treatment, an adjustment of medication was needed for 35.8% of patients, mainly for antihypertensive and statins therapies. During the study period, 3 patients discontinued therapy (2.5%).

The ITT analyses showed a SVR12 of 88.3%, while 95.5% per protocol of the study population achieved SVR12. Five relapsers were seen: three of them were treated with an IFN-based regimen, all of them before SVR12. There are 9 patients with missing data of SVR12: 3 cases were related to the diagnosis of another illness (2 HCC and 1 cholangiocarcinoma); 1 case because the patient is in the follow-up (FU) period, as the study period concluded before SVRS12; for 3 cases because there were lost to FU of these patients and 2 patients died. No associated factor was linked to treatment failure.

The study population had an adherence to therapy over 80% in 97.3% of cases. Adherence was carefully recorded by validated tests, an indirect method of recount of the study medication: Adherence% = [(Dispensed medication – Returned medication)/Prescription medication] × 100.

Two patients died during the study period. One patient died two months after end of treatment related to subdural hematoma. The other patient was a 69-year-old female with compensated cirrhosis, who died of unknown causes during treatment with SOF + LDV on week 20.

5. Discussion

This study evaluates the safety and efficacy of different DAAs based therapies among mono-infected CHC elderly patients in clinical follow-up in Spain. The SVR12 per ITT was 88.3%. Although the number of elderly patients in our cohort treated with the different new regimens, it does not allow us to conclude which are the most tolerated regimens.

This study identifies RBV and PI as the most likely drugs to cause AE. In this cohort, when a PI is part of the regimen, AE were three times more frequent, independently of RBV use. No patient treated with RBV and DAAs stopped medication due to AE [12]. Three patients who discontinued treatment were getting a PI based therapy: 2 cases in combination with Peg-IFN and other development a HCC. Therefore, we did not find any association between PI-based therapies and discontinuations.

Overall, the SVR12 was high, even for the first generation of PI. Of note, in this population the use of Peg-IFN had a negative impact in the SVR12; three of the five patients who failed were on Peg-IFN based regimes, nowadays contraindicated for this special population. Prior to advent of DAA based regimens, differences in terms of SVR12 between elderly and non-elderly patients could have been influenced by low tolerance to Peg-IFN + RBV regimens [13]. At present, there are several results from clinical trials using DAAs [14], recognising similar SVR12 in both age groups and are very similar rates of SVR observed in this study.

Two patients were diagnosed with HCC during treatment. A recent study shows an increased tendency to develop an HCC after HCV treatment initiation, using DAAs in patients who have already been cured of a previous occurrence. At this moment, any conclusion should be made and we need to be cautious with these results [15].

There is scarce data about the clinical evolution in elderly patients after HCV cure [16]. Several mathematical natural history models predict an increasing tendency in liver decompensation and deaths related to HCV over the next 10 years [17] ; [18]. However, this tendency might be modified with the recent introduction of DAAs.

In this context, there is a lack of data in relation to the cost-effectiveness of treatment with DAAs in elderly patients [19]. More studies must be conducted to clarify the benefits of these therapies in this special population.

There are some limitations in this study that might be considered. There are included IFN and no IFN-based regimens, where tolerance, adherence and rates of SVR12 have huge differences. The sample size and the short FU period does not allow to conclude differences in prognosis.

In conclusion, elderly patients achieved high rates of SVR12 with DAAs regimens. However, AE and modification of chronic medications make these patients a special population, where we had to exercise more care.

Conflicts of interest
All authors declare no conflicts of interest.

Funding
This work was supported in part by grants from Fondo de Investigación Sanitaria (CPII14/00014, PI10/02166, PI13/02266, CM15/00233) and Fundación Profesor Novoa Santos, A Coruña.

Ethical approval
The study protocol was reviewed and approved by a Medical Ethics Committee and this publication is in accordance with the community standards. All the study participants were informed before the study inclusion.

Acknowledgments
We would like to thank Biobank of A Coruña (SERGAS) for providing us the technical, ethical and legal advice necessary for the development of our research. We also thank the collaboration of Josefina Baliñas (HIV and Viral Hepatitis Unit, Complejo Hospitalario Universitario A Coruña).

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