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# The efficacy and safety of direct acting antiviral treatment and clinical significance of drug–drug interactions in elderly patients with chronic hepatitis C virus infection

J. Vermehren, K.-H. Peiffer, C. Welsch, G. Grammatikos, M.-W. Welker, N. Weiler, S. Zeuzem, T. M. Welzel & C. Sarrazin

Medizinische Klinik 1, Universitätsklinikum Frankfurt, Frankfurt am Main, Germany.

**Correspondence to:**
Dr J. Vermehren, Medizinische Klinik 1, Universitätsklinikum Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany.
E-mail: Johannes.Vermehren@kgu.de

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## SUMMARY

### Background
Direct antiviral therapies for chronic hepatitis C virus (HCV) infection have expanded treatment options for neglected patient populations, including elderly patients who are ineligible/intolerant to receive interferon (IFN)-based therapy.

### Aim
To investigate the efficacy, tolerability and potential for drug–drug interactions (DDIs) of IFN-free treatment in patients aged ≥65 years in a large real-world cohort.

### Methods
A total of 541 patients were treated with different combinations of direct antiviral agents (DAAs: ledipasvir/sofosbuvir ±ribavirin; daclatasvir/sofosbuvir ±ribavirin; paritaprevir/ombitasvir ±dasabuvir ±ribavirin or simeprevir/sofosbuvir ±ribavirin in genotype 1/4, and daclatasvir/sofosbuvir ±ribavirin or sofosbuvir/ribavirin in genotype 2/3). Efficacy, safety and potential DDIs were analysed and compared between patients aged <65 years ($n$ = 404) and patients aged ≥65 years ($n$ = 137) of whom 41 patients were ≥75 years.

### Results
Sustained virological response rates were 98% and 91% in patients aged ≥65 years and <65 years, respectively. Elderly patients took significantly more concomitant medications (79% vs. 51%; $P < 0.0001$). The number of concomitant drugs per patient was highest in patients ≥65 years with cirrhosis (median, three per patient; range, 0–10). Based on the hep-druginteractions database, the proportion of predicted clinically significant DDIs was significantly higher in elderly patients (54% vs. 28%; $P < 0.0001$). The number of patients who experienced treatment-associated adverse events was similar between the two age groups (63% vs. 65%; $P$ = n.s.).

### Conclusions
Elderly patients are at increased risk for significant DDIs when treated with DAAs for chronic HCV infection. However, with careful pre-treatment assessment of concomitant medications, on-treatment monitoring or dose-modifications, significant DDIs and associated adverse events can be avoided.




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## INTRODUCTION

Chronic infection with the hepatitis C virus (HCV) is a major health burden worldwide and approximately 500 000 people die each year from HCV related liver diseases.[1]

According to estimates by the Centers for Disease Control (CDC), elderly persons are disproportionally affected by HCV and despite the recent approval of highly efficient direct antiviral agents (DAAs) the rates of cirrhosis and hepatocellular carcinoma are predicted to rise in the near future.[2]

Age has been a major limitation of interferon-based treatment, mainly due to increasing prevalence of comorbidity, poor tolerability and overall reduced efficacy in this population.[3] Patients aged 65 years and older were mostly excluded from clinical trials while large-scale real-world database studies showed lower sustained virological response rates and higher withdrawal rates due to side effects in this patient population.[4]

With the recent approval of all-oral DAAs, treatment access has expanded to interferon ineligible/intolerant patient populations, including persons of older age. However, despite the overall excellent tolerability of interferon-free DAA combination therapies, elderly patients, especially those aged 75 years and older were again excluded from most clinical trials.[5–8] In a recent retrospective analysis of four phase 3 trials of the HCV NS5A inhibitor ledipasvir plus the HCV polymerase inhibitor sofosbuvir in patients with HCV genotype 1 infection, only 24/2293 (1%) of the study population were aged 75 or older.[9]

Given the fact that current HCV treatment regimens are both more efficient and better tolerated than interferon-based therapies, the number of elderly patients who will receive anti-HCV treatments is likely to increase. Whether the increased prevalence of comorbidity and concurrent medications in elderly patients is associated with higher rates of adverse events and/or treatment failure is not known. Moreover, the use of ribavirin in these patients may pose a greater risk for associated side effects such as cough, rash and haemolytic anaemia.[10]

In this study, we aimed to assess the efficacy and safety of DAA regimens as well as the clinical significance of potential drug–drug interactions with concomitant medications in patients aged ≥65 years (including subgroup analysis of patients ≥75 years) in a large real-world cohort.

## METHODS

### Study cohort

Consecutive patients who presented to our outpatient clinic for treatment of chronic HCV infection after the approval of sofosbuvir (January 2014) until September 2015 were included in the analysis. Patients with HIV and/or HBV co-infection and patients with previous solid organ transplantation (kidney, liver, pancreas) were excluded. Patients who received pegylated interferon as part of their treatment regimen and those who received DAA combinations that are currently no longer recommended (e.g. sofosbuvir and ribavirin in HCV genotype 1) were also excluded.

Thus, all patients received one of the following five regimens: (i) sofosbuvir (SOF; nucleoside NS5B polymerase inhibitor) and ledipasvir (LDV; NS5A inhibitor) ± ribavirin (RBV) in genotypes 1, and 4–6, (ii) SOF and daclatasvir (DCV; NS5A inhibitor) ± RBV in genotypes 1 and 3, (iii) paritaprevir/ritonavir (PTV; ritonavir boosted protease inhibitor), ombitasvir (OBV; NS5A inhibitor) and dasabuvir (DSV; non-nucleoside NS5B polymerase inhibitor) ± RBV in genotype 1 (3D regimen), (iv) SOF and simeprevir (SMV; NS3 protease inhibitor) ± RBV in genotype 1 and (v) SOF + RBV in genotypes 2 and 3. RBV was administered based on current guideline recommendations.[11, 12] RBV dose adjustments were done according to the label recommendations.

### Assessment of baseline and treatment-related patient parameters

Demographic baseline parameters, concomitant medications, laboratory tests as well as safety and efficacy data were retrospectively and anonymously analysed from electronic hospital charts. Efficacy was assessed at 12 weeks after the end of treatment. A sustained virologic response (SVR) was defined as negative HCV RNA at this time point.

### Definition of old age

Patients of old age were defined as being 65 years and older. This population can be divided into the young-old (ages 65–74), the old-old (ages 75–84), and the oldest-old (85 years and older) as previously described.[13]

Baseline and efficacy data as well as safety and clinical significance of drug–drug interactions were assessed in patients aged 65 years and older. Comparisons were made between groups of patients aged ≥65 years and <65 years. Subgroup analyses were performed for

patients aged 75 years and older (old-old and oldest-old combined). No subgroup analysis was performed for the only patient aged 86 years.

### Assessment of drug–drug interactions (DDIs) and treatment modifications

A web-based tool developed by the University of Liverpool (available at www.hep-druginteractions.org) was used for risk assessment of potential drug–drug interactions (DDIs) based on patients concomitant medications and the respective antiviral regimen. The DDI database is free for use. Interactions can be assessed by first choosing one or more DAAs from a context menu followed by choosing one or more combination drugs or drug classes. A summary of results and detailed descriptions are displayed hereafter. In addition, the respective prescribing information was also used (as of January 2016).

Potential DDIs were assigned to distinct risk categories according to the predicted level of significance (based on hep-druginteractions.org nomenclature); that is, 0 = interaction has not been assessed; 1 = no clinically significant interaction expected; 2 = potential interaction that may require close monitoring, alteration of drug dosage or timing of administration; 3 = co-administration either not recommended or contraindicated. Thus, category 2 and 3 DDIs were considered clinically significant. Outpatient medications with category 3 DDIs were either stopped prior to antiviral therapy or a different DAA regimen was chosen.

In patients taking medications with category 2 DDIs, the respective drugs were either stopped, dose-modified or closely monitored, as previously recommended.[14]

### Calculation of glomerular filtration rate

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used for estimating the glomerular filtration rate (GFR) in this study. The CKD-EPI equation uses a 2-slope 'spline' to model the relationship between GFR and serum creatinine, age, sex and race.[15]

### Assessment of ribavirin-induced haemolytic anaemia

The occurrence of RBV induced haemolytic anaemia was assessed at treatment weeks 2, 4, 8 and 12 relative to the baseline haemoglobin level.

Significant anaemia was defined as an absolute decline in haemoglobin levels <10 g/dL and/or a decline of greater than 3 g/dL. Ribavirin dose reductions were made according to the manufacturer's recommendations and no erythropoetin was used in this study.

### Statistics

All statistical analyses were performed using GraphPad Prism version 5 for Mac (La Jolla, CA, USA). Descriptive statistics are shown as mean ± s.d. or median and range. Comparisons between groups were made using parametric *t*-tests or nonparametric Mann–Whitney *U*-tests, where appropriate. $P < 0.05$ were considered statistically significant.

### Ethics

The study was conducted according to the declaration of Helsinki. The ethics committee of the University Hospital Frankfurt approved the retrospective analysis of anonymous patient data.

## RESULTS

### Baseline characteristics

A total of 541 patients treated with all-oral DAA combination regimens were included in this study. One hundred and thirty-seven subjects were aged 65 years and older. Of these, 96 were aged 65–74 years, 40 were aged 75–84 years and one patient was 86 years old at the start of antiviral therapy.

Among patients aged ≥65 years, the mean age was 71 years (range, 65–86 years), 47% were men ($n$ = 66/137), genotype 1b was the predominant HCV subtype ($n$ = 84/137; 61%) and 47% ($n$ = 64/137) had cirrhosis. The majority ($n$ = 76/137; 56%) of patients aged ≥65 years had failed a prior course of interferon-based therapy. Baseline characteristics of the total study population according to age groups are shown in Table 1.

### Treatment regimens and efficacy

The distribution of treatment regimens across the different age groups is shown in Table 2.

Overall, SVR was achieved by 98% ($n$ = 134/137) of patients aged 65 years and older. There was no virological treatment failure in patients who received at least 80% of the intended treatment duration and the SVR rate in these patients was 100% ($n$ = 134/134).

Two patients stopped treatment prematurely and one patient died during treatment and the cause of death was considered unrelated to the antiviral treatment (see below). Two patients aged ≥65 years discontinued treatment prematurely: One GT1b patient treated with LDV/SOF discontinued all medications after 2 weeks due to acute kidney injury, and one GT1b patient treated with PTV/OBV +DSV +RBV discontinued all medications after 1 week due to grade 3 hyperbilirubinaemia. This patient was later

**Table 1 |** Demographic and clinical characteristics of the study cohort ($n$ = 541)

| | <65 years $n$ = 404 | ≥65 years $n$ = 137 | 65–74 years $n$ = 96 | ≥75 years $n$ = 41 |
|---|---|---|---|---|
| Mean age (range) | 51 (18–64) | 72 (65–86) | 69 (65–74) | 78 (75–86) |
| Male gender, $n$ (%) | 252 (62) | 64 (47) | 46 (48) | 18 (44) |
| HCV Genotype*, $n$ (%) | | | | |
| 1a | 124 (31) | 36 (26) | 26 (27) | 10 (24) |
| 1b | 171 (42) | 84 (61) | 58 (61) | 26 (64) |
| 2/3 | 83 (21) | 15 (11) | 10 (10) | 5 (12) |
| Other | 26 (6) | 2 (2) | 2 (2) | – |
| Cirrhosis, $n$ (%) | 157 (39) | 64 (47) | 40 (42) | 24 (59) |
| Treatment experienced, $n$ (%)* | 229 (57) | 76 (55) | 55 (57) | 21 (51) |
| Mean HCV RNA [$log_{10}$] (SD) | 6.0 (0.8) | 6.1 (0.6) | 6.1 (0.7) | 6.1 (0.5) |
| Mean eGFR [mL/min] (SD) | 97.5 (16.7) | 76.5 (17.4) | 78.9 (17.3) | 70.3 (16.5) |
| Mean haemoglobin [g/dL] female/male (SD) | 14.8 (1.8)/13.7 (1.3) | 13.4 (1.6)/14 (1.9) | 13.9 (1.9)/13.5 (1.4) | 13.1 (1.8)/14.2 (2.0) |

eGFR, estimated glomerular filtration rate; SD, standard deviation.

* Treatment experienced = nonresponse or relapse to prior peg-Interferon/ribavirin therapy.

**Table 2 |** Treatment regimens according to age groups (patients aged 65 years and older are subdivided into patients aged 65–74 years and patients aged 75 years and older)

| Treatment regimen, $n$ (%) | <65 years ($n$ = 404) | ≥65 years ($n$ = 137) | 65–74 years ($n$ = 96) | ≥75 years ($n$ = 41) |
|---|---|---|---|---|
| SOF/LDV ±RBV | 185 (46) | 68 (50) | 48 (50) | 20 (48) |
| SOF +DCV ±RBV | 75 (19) | 21 (15) | 12 (13) | 9 (22) |
| PTV/OBV ±DSV ±RBV | 57 (14) | 22 (15) | 18 (19) | 4 (10) |
| SOF +SMV ±RBV | 46 (11) | 13 (10) | 9 (9) | 4 (10) |
| SOF +RBV | 40 (10) | 13 (10) | 9 (9) | 4 (10) |

SOF, sofosbuvir; LDV, ledipasvir; RBV, ribavirin; DCV, daclatasvir; PTV, paritraprevir; OBV, ombitasvir; DSV, dasabuvir; SMV, simeprevir.

diagnosed with gilbert's syndrome, which most likely explains the unusually high PTV-associated hyperbilirubinaemia. Both patients had positive HCV RNA during follow-up. One patient died during the treatment period. The cause of death (multi-organ failure following haemorrhagic shock after femoral arterial catheterisation) was considered unrelated to the DAA therapy.

SVR was observed in 91% ($n$ = 369/404) of patients <65 years. A total of 21 patients experienced virological relapse or nonresponse. Two patients stopped treatment prematurely: One patient discontinued treatment because of worsening of pre-existing depression after 6 weeks and one patient discontinued treatment after 4 weeks because of debilitating fatigue. Eleven patients were lost to follow-up during or after antiviral therapy. One patient died during the treatment period. The cause of death (multi-organ failure following haemorrhagic shock after variceal bleeding) was considered unrelated to the DAA therapy.

If only patients <65 years of age with known virological outcome and who received at least 80% of the intended treatment duration were considered, the SVR rate was 95% ($n$ = 369/390; see Figures 1 and 2 for an overview of SVR rates according to genotypes, age and treatment regimen).

All genotypes and treatment regimens were affected by virological failure: LDV/SOF ± RBV ($n$ = 4), SOF and DCV ± RBV ($n$ = 6), PTV/OBV + DSV ($n$ = 2), SOF and SMV ± RBV ($n$ = 6) and SOF + RBV ($n$ = 3).

## Frequencies of concomitant medications

A total of 152 different concomitant medications were taken by the patients in our study cohort ($n$ = 81 in patients ≥65 years). The most common drug classes that

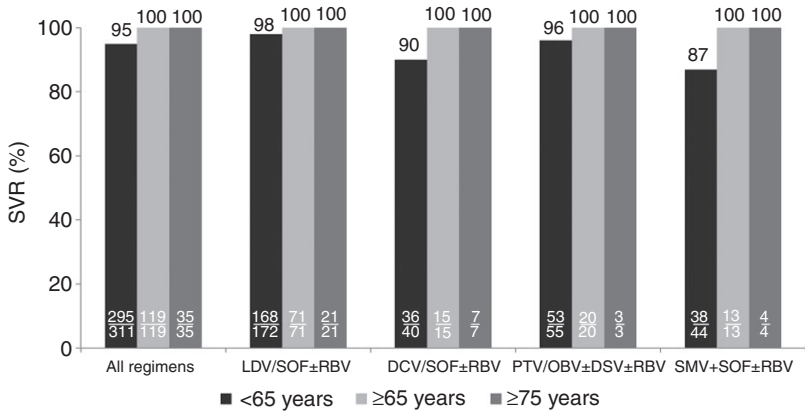


**Figure 1 |** SVR rates in patients with HCV genotype 1/4 infection ($n$ = 430) according to treatment regimen and age groups. Only patients who completed ≥80% of the intended treatment duration and who had a known virological outcome are included. Treatment regimens included the following: ledipasvir/sofosbuvir ±ribavirin (LDV/SOF±RBV), daclatasvir +sofosbuvir ±ribavirin (DCV+SOF±RBV), paritaprevir/r/ombitasvir±dasabuvir ±ribavirin (PTV/OBV±DSV±RBV) and simeprevir +sofosbuvir ±ribavirin (SMV+SOF±RBV). SVR data are shown for patients <65 years vs. patients ≥65 years of age. In addition, a subgroup analysis is shown for patients ≥75 years of age.

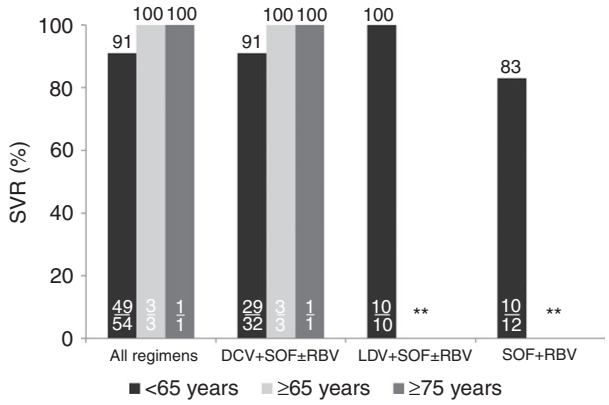


**Figure 2 |** SVR rates in patients with HCV genotype 3 infection ($n$ = 57) according to treatment regimen and age groups. Only patients who completed ≥80% of the intended treatment duration and who had a known virological outcome are included. Treatment regimens included the following: daclatasvir +sofosbuvir ±ribavirin (DCV+SOF±RBV), ledipasvir/sofosbuvir ±ribavirin (LDV/SOF ±RBV), and sofosbuvir +ribavirin (SOF+RBV). SVR data are shown for patients <65 years vs. patients ≥65 years of age. In addition, a subgroup analysis is shown for patients ≥75 years of age. **no patients aged 65 years and older were treated with LDV/SOF or SOF+RBV.

were taken by >5% of the study cohort included proton pump inhibitors (10%), nonselective beta-blocking agents (9%), thyroid hormones (8%), loop diuretics (8%), angiotensin-converting enzyme inhibitors (8%), vitamin D supplements (7%), selective beta-blocking agents (6%) and insulin preparations (5%).

Overall, the number of patients who took concomitant medications was significantly higher in patients aged ≥65 years compared to <65 years (79% vs. 51%; $P < 0.0001$). Furthermore, the number of patients who took 4 or more regular concomitant medications was significantly higher in patients ≥65 years compared to <65 years (34% vs. 17%; $P < 0.0001$).

In patients <65 years, the median number of drugs per patient was 1 (range, 0–12). In patients ≥65 years, the median number of drugs per patient was 2 (range, 0–10). In patients ≥75 years vs. 65–74 years, the number of drugs per patients was not different.

The median number of drugs per patient was increased in patients ≥65 years who also had cirrhosis (3; range, 0–10). In cirrhotic patients ≥75 years, the median number of drugs was higher compared to patients without cirrhosis (median no. of drugs, 3 vs. 2).

## Potential for drug–drug interactions between DAAs and concomitant medications

Based on DDI risk classification from the hep-druginteractions.org database, category 2/3 DDIs were predicted for 35% ($n$ = 189/541) of the total study population (60% of patients with concomitant medications).

The proportion of predicted category 2/3 DDIs was significantly higher in patients ≥65 years compared to patients <65 years (54% vs. 28%; $P < 0.0001$). There was no difference in category 2/3 DDIs between patients aged

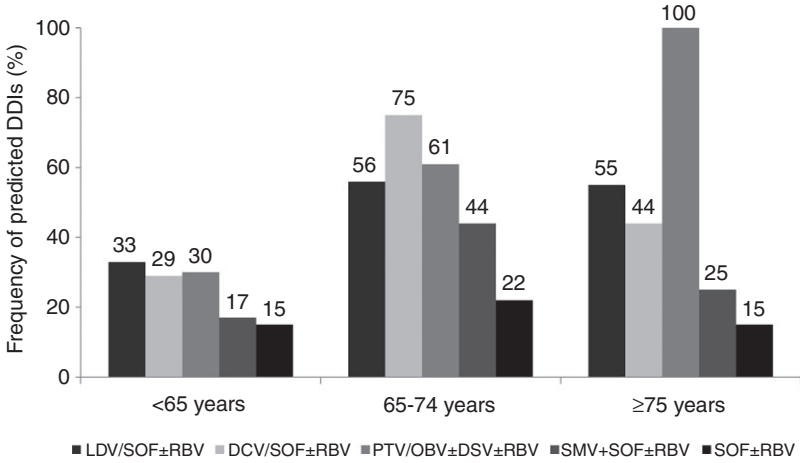


**Figure 3 |** Frequencies of predicted clinically significant drug–drug interactions (defined as category 2/3 interactions according to the hep-druginteractions.org database) between concomitant medications and antiviral therapy according to treatment regimen and age groups ($n$ = 541). All listed patients had ≥1 drug of concomitant medications predicted to cause DDIs.

65–74 years vs. ≥75 years (55% vs. 51%; $P$ = N.S.). The frequencies of potentially clinically significant DDIs (category 2/3) according to age and DAA regimen are shown in Figure 3.

For patients treated with LDV/SOF±RBV, the most common concomitant drug classes involved in potentially significant DDIs (DDI category 2/3) were beta-blocking agents in 16% ($n$ = 30/185) and 34% ($n$ = 23/68) and proton pump inhibitors in 11% ($n$ = 21/185) and 25% ($n$ = 16/68) of patients <65 and ≥65 years of age respectively. For patients treated with DCV+SOF±RBV, the most common concomitant medications at risk for significant interactions were beta-blocking agents in 19% ($n$ = 14/75) and 29% ($n$ = 6/21) and thyroid hormones in 11% ($n$ = 8/75) and 24% ($n$ = 5/21) of patients <65 and ≥65 years of age respectively. For patients treated with PTV/OBV±DSV±RBV, significant interactions were primarily expected for thyroid hormones in 12% ($n$ = 7/57) and 45% ($n$ = 10/21) and alfa- and beta-blocking agents in 14% ($n$ = 8/57) and 23% ($n$ = 5/22) of patients <65 and ≥65 years of age respectively. Finally, for SMV-containing regimens, the most common drug classes at risk for clinically significant interactions were beta-blocking agents in 13% ($n$ = 6/46) of patients <65 years and statins that were co-administered in 15% ($n$ = 2/13) of patients ≥65 years of age.

The most common concomitant medications with potential category 2/3 DDIs and respective action taken before and during antiviral therapy to avoid such DDIs are shown in Table 3.

## Safety and adverse events

The occurrence of adverse events was documented in 77% ($n$ = 417/541) of patients. A total of 63% ($n$ = 264/417) patients experienced at least one adverse event during the treatment period. Adverse events were generally mild and the number of adverse events was not significantly different between patients <65 years and patients ≥65 years respectively (63% vs. 65%; $P$ = N.S.). We observed no significant increase in adverse events potentially related to DDIs (e.g. dizziness, bradycardia or GI disturbances in patients with concomitant carvedilol treatment; TSH changes in patients treated with levothyroxine).

The most common adverse events were fatigue (35% and 37%), dyspnoea (11% and 15%; only patients on RBV treatment affected), headache (22% and 11%), pruritus (7% and 10%), rash (7% and 2%) and insomnia (6% and 7%) in patients <65 and ≥65 years of age respectively.

## Estimated glomerular filtration rate (eGFR)

At baseline, the eGFR (CKD-EPI) was 97.5 mL/min for patients <65 and 76.5 mL/min for ≥65 years of age ($P$ < 0.0001). The eGFR in patients between 65 and 74 years was 78.9 mL/min and 70.3 mL/min in patients ≥75 years of age ($P$ = 0.0038). For all age groups and treatment regimens with and without SOF, eGFR values showed no significant changes over the course of antiviral treatment ($P$ = N.S.).

**Table 3 |** Description of potential drug–drug interactions (DDIs) with commonly used co-medications in patients with chronic HCV infection. The colour scheme represents a traffic light labelling system to highlight the signficance level of expected DDIs according to the hep-druginteractions.org website: green = no DDI expected; amber = potential DDI expected; red = co-administration not recommended/contraindicated. Suggested actions that should be taken to avoid DDI-related adverse events are also given.

| Drug category | LDV/ SOF±RBV | DCV/ SOF±RBV | OBV/PTV/ R±DSV | SMV/ SOF±RBV | SOF/RBV |
|---|---|---|---|---|---|
| Proton pump inhibitors (e.g. omeprazole, pantoprazole) | | | | | |
| DDI | ↓LDV exposure | – | ↓PPI exposure | – | – |
| Action taken | ↓dose to 20 mg/ simultaneous administration req. | None | ↑dose of PPI if necessary | None | None |
| Thyroid hormones (levothyroxine) | | | | | |
| DDI | – | ↑levothyroxine exposure* | ↑levothyroxine exposure* | – | – |
| Action taken | None | Monitor/↓dose if necessary | Monitor/↓dose if necessary | None | None |
| Selective β-blockers (BB; e.g. bisoprolol, metoprolol) | | | | | |
| DDI | ↑BB exposure (only in severe hepatic impairment)* | ↑BB exposure (only in severe hepatic impairment)* | ↑bisoprolol exposure (CYP3A4 inhib. by R)* | ↑bisoprolol exposure (CYP3A4 inhib. by SMV)* | ↑BB exposure (only in severe hepatic impairment)* |
| Action taken | None† | None† | ↓dose if necessary | ↓dose if necessary | None† |
| Nonselective β-blockers (NSBB; e.g. carvedilol, propranolol) | | | | | |
| DDI | ↑carvedilol + LDV exposure*,‡ | ↑carvedilol + DCV exposure*,‡ | ↑carvedilol exposure*,‡ | ↑carvedilol + SMV exposure*,‡ | ↑SOF exposure* |
| Action taken | ↓carvedilol dose if necessary | ↓carvedilol dose if necessary | Monitor blood pressure/heart rate | ↓carvedilol dose if necessary | None (metabolite GS-331007 is not increased) |
| Statins (e.g. simvastatin, pravastatin) | | | | | |
| DDI | ↑statin exposure*,§ | ↑statin exposure*,§ | ↑statin exposure¶ | ↑statin exposure§ | – |
| Action taken | ↓statin to lowest dose | Monitor/↓statin dose if necessary | ↓pravastatin to lowest dose (other statins contraindicated) | ↓statin to lowest dose | None |
| Calcium channel blockers (e.g. amlodipine) | | | | | |
| DDI | ↑amlodipine + LDV exposure* | ↑DCV exposure* | ↑amlodipine exposure | ↑amlodipine + SMV exposure* | ↑SOF exposure* |
| Action taken | Monitor blood pressure/heart rate | Monitor | ↓amlodipine dose by 50% | Monitor blood pressure/heart rate | None |

LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; DCV, daclatasvir; OBV, ombitasvir; PTV/R, paritaprevir/ritonavir, SMV, simeprevir; ↑, increase; ↓, decrease.

* Co-administration has not been studied.

† Dose reduction may be necessary in patients with severe hepatic impairment.

‡ Side effects of increased carvedilol exposure may include dizziness, bradycardia and GI disturbances.

§ Side effects of increased statin exposure may include muscle pain and CK elevation.

### Ribavirin-induced anaemia

RBV was co-administered in 42% ($n$ = 168/404), 43% ($n$ = 59/137) and 49% ($n$ = 20/41) of patients <65 years, ≥65 years and ≥75 years of age respectively. Significant anaemia occurred in 34% ($n$ = 20/59) and 35% ($n$ = 7/20) of ≥65 years and ≥75 years of age respectively.

The rates of patients aged ≥65 years who experienced at least one adverse event (any event) were 68% ($n$ = 40/59) and 32% ($n$ = 25/78) with and without RBV respectively. In patients aged ≥75 years, these rates were 70% ($n$ = 14/20) and 38% ($n$ = 8/21) with and without RBV respectively. Side effects typically associated with RBV use, including haemolytic anaemia, skin rash and cough were observed in 42% ($n$ = 25/59) and 55% ($n$ = 11/21) of patients ≥65 years and ≥75 years of age respectively.

## DISCUSSION

Until recently, treatment options in elderly patients with chronic HCV infection were limited, mainly due to contraindications and side effects associated with IFN-based therapies.[3] Moreover, lower SVR rates and higher rates of treatment discontinuation were reported.[4, 16–18] The recent approval of highly effective IFN-free regimens has led to a paradigm change with improved options for difficult-to-cure patients, including those of older age.[19] Interestingly, despite improved safety profiles of all-oral DAA treatments, elderly patients were once again excluded from most clinical trials. Despite this, a recent retrospective analysis of the LDV/SOF approval trials showed high SVR rates in patients ≥65 years of age.[9] However, older patients represented a mere 12% of the total study population and the proportion of patients aged 75 years and older was only 1% ($n$ = 24).

In our retrospective study, we included a large proportion of elderly patients (25%). The different combinations of all-oral DAA therapies showed comparable efficacy in patients aged ≥65 years and younger patients. Moreover, when specifically looking at genotype 1 patients treated with the currently most widely used regimens (LDV/SOF ±RBV or PTV/OBV +DSV ±RBV), SVR rates exceeded 95% in both age cohorts, and this was also true in the subgroup of patients ≥75 years of age. While DAA treatment seems to be feasible in virtually all patients regardless of age and comorbidities, the question arises whether old patients should always be considered for antiviral therapy. On the one hand, progression to cirrhosis has been shown to be an age-dependent process.[20] However, given the high costs of current DAA regimens, treatment priority should clearly be given to patients with advanced liver disease whereas treatment is not recommended in patients with limited life expectancy.[12] Obviously, the decision to treat elderly patients or not is greatly influenced by local guidelines and/or reimbursement policies as well as societal considerations. On the other hand, if cirrhosis is not present in elderly patients despite a long history of HCV infection, progression to cirrhosis may never occur. In our study, 41% of patients aged 75 and older had no cirrhosis at the time of DAA treatment. Thus, prevention of fibrosis progression was not the main driver for treatment initiation in these patients. Indeed, only a mild disease progression has been observed in several studies, particularly in women, despite a long history of HCV infection.[21, 22] However, despite this favourable course of disease, high levels of psychological distress and impaired quality of life due to debilitating fatigue may still be present in many of these patients.[21] Presence of such factors and other extrahepatic manifestations which have been shown to increase with age[23] may justify the decision to treat older patients, even in case advanced liver disease is not present. This is supported by recent data that suggest that DAA therapies are associated with significantly improved patient-reported outcomes and even favourable short-term health economic outcomes.[24, 25]

While more and more patients are being treated for HCV infection outside of clinical trials, the risk for potentially serious DDIs is increasing.[14] In our study, older patients took significantly more concomitant medications, which reflects the increasing morbidity in the ageing HCV population.[26] Moreover, our study showed that the number of drugs taken by an individual patient was highest in patients aged 65 and older who also had cirrhosis. This may be attributable to the particularly high number of cardiovascular drugs and diuretics in this population.

Management of potential DDIs had become particularly important after the approval of the first-generation protease inhibitors telaprevir and boceprevir which are strong inhibitors and substrates of the P-glycoprotein (P-gp) and cytochrome P450 3A4.[27, 28] This led to a greater awareness of potential DDIs in patients treated for HCV infection. Consequently, a DDI website was launched by the University of Liverpool in 2010 that provides a comprehensive DDI database (www.hep-druginteractions.org) that is free for use.

Currently recommended DAAs still show some interactions with P-gp and cytochrome P450 enzymes, albeit only to a much lesser extent than telaprevir and boceprevir.[27]

Our study had a high proportion of patients taking concomitant medications that could potentially lead to significant DDIs during antiviral therapy. The predicted proportion of potentially significant DDIs was particularly high in elderly patients. More than half of elderly patients were predicted to have significant DDIs. Interestingly, all

DAA regimens were affected by potentially significant DDIs. In elderly patients, the risk was highest in patients treated with DCV and SOF whereas similar frequencies of potential DDIs were predicted for patients treated with LDV/SOF and the OBV/PTV+DSV regimen.

Proton pump inhibitors (PPIs) have recently been associated with a higher risk of virological failure in patients treated with LDV/SOF.[29] The negative impact of PPIs, however, does not seem to derive from true DDIs but changes in drug absorption.[30] Simultaneous administration of PPIs resulted in only slightly decreased LDV AUC and Cmax that were not judged to be clinically relevant. In contrast, co-administration of PPIs and PTV/ritonavir significantly decreased omeprazole AUC and Cmax due to induction of CYP2C19 by ritonavir which may lead to decreased PPI efficacy.[31]

In our study, actions were taken to reduce the impact of potentially significant DDIs as previously proposed.[14] However, for many concomitant medications, no reliable prediction for potential DDIs is available because of the lack of clinical data. Here, potential DDIs are predicted based upon metabolic pathway interactions. This emphasises the need for comprehensive pharmacovigilance networks to meet the challenges of treating elderly and/or multimorbid patients.

In our study, no significant adverse events attributable to DDIs were noted. Indeed, despite the higher number of drugs taken and the higher frequency of predicted DDIs in elderly patients, the number of adverse events was not different between the two age groups. This may again be attributable to the meticulous DDI assessment before treatment initiation and careful monitoring thereafter. In addition, although the use of RBV increased the number of adverse events particularly in elderly patients, significant anaemia was not higher than in younger patients.

Our study has several limitations, including the retrospective design and the heterogeneous number of treatment regimens. However, this is currently the largest real-world DAA experience among elderly patients that also assesses the potential clinical impact of DDIs.

In conclusion, our study shows that all approved IFN-free DAA regimens are highly effective in elderly patients, especially those aged 75 years and older, while concomitant drugs pose a risk for potentially serious DDIs. Use of a free accessible Internet-database and careful management during therapy can effectively prevent DDI-associated adverse events and treatment failure.

## AUTHORSHIP

*Guarantor of the article*: JV.
*Author contributions*: JV, CW and CS contributed to the study design and concept. All authors contributed to the acquisition of data and reviewed versions of the manuscript and provided critical comments. JV interpreted the data and drafted the manuscript. All authors approved the final version of the manuscript.

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