Clinical studies on hepatitis B, C, and E virus infection
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Citation for published version (APA):

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CHAPTER 5

Sofosbuvir plus Simeprevir for the Treatment of HCV Genotype 4 Patients with Advanced Fibrosis or Compensated Cirrhosis is Highly Efficacious in Real-Life


*Journal of Viral Hepatitis* 2016; 23(12): 950–954
ABSTRACT

Introduction
Chronic hepatitis C virus (HCV) infection is a major cause of chronic liver disease and liver-related death. Recently, multiple regimens of different direct-acting antiviral agents (DAA’s) have been registered. Although treatment with sofosbuvir (SOF) and simeprevir (SMV) is registered for the treatment of genotype 4 patients in some countries, data on efficacy of this combination is lacking. We aimed to assess the efficacy of SOF and SMV with or without RBV during 12 weeks in a real-life cohort of genotype 4 HCV patients.

Patients and Methods
A retrospective multi-center observational study was conducted in 4 hospitals in Amsterdam, the Netherlands, including patients with advanced liver fibrosis or liver cirrhosis treated with SOF plus SMV with or without RBV during 12 weeks for a genotype 4 chronic HCV infection from 1/1/2015 to 1/8/2015. Sustained Viral Response (SVR) was established at week 12 after end of treatment.

Results
A total of 53 patients with genotype 4 HCV infection, treatment naïve and experienced, were included. SVR was achieved in 49/53 patients (92%). The four failures all had a virological relapse and did not receive ribavirin. Three were non-responder to earlier interferon-based treatment and one was treatment-naive.

Conclusions
In this real-life cohort of patients with HCV genotype 4 infection and advanced liver fibrosis/cirrhosis we show that treatment with SOF and SMV is effective. The addition of RBV could be considered in treatment-experienced patients as recommended in guidelines.
INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major cause of chronic liver disease. It causes liver fibrosis and may ultimately lead to liver cirrhosis, hepatocellular carcinoma and death. It is estimated that there are around 80 million people worldwide with chronic HCV infection.

Recently, new potent all-oral antiviral treatment regimens resulting in very high cure rates in all HCV genotypes were registered. For patients with hepatitis C genotype 4 the combination of sofosbuvir (SOF) and simeprevir (SMV) is recommended in European guidelines as one of the treatment indications. Although various studies in genotype 1 chronic hepatitis C (CHC) patients reported sustained viral response (SVR) rates of > 90% after treatment with SOF and SMV for 12 weeks with or without ribavirin (RBV), data in genotype 4 CHC are lacking. This recommendation in the guidelines is based on study results from SOF or SMV combined with both peginterferon (PegIFN) and RBV and SOF/RBV showing similar results in HCV genotype 1 and 4 patients. EASL recommendations state that given the effectiveness of both SOF and SMV against HCV genotype 4, it is likely that the results of combination therapy with SOF and SMV in HCV genotype 1 patients can be extrapolated. This statement has also been followed in the Dutch guidelines. Whether RBV should be added to this treatment regimen is unknown. Recent studies in HCV genotype 1 cirrhotic patients treated with SOF/SMV with or without ribavirin, contradicted each other in the value of the addition of RBV.

Our aim was to assess in real-life the efficacy of combination treatment of SOF and SMV with or without RBV during 12 weeks for HCV genotype 4 patients.

PATIENTS AND METHODS

We conducted a retrospective multi-center observational study in two large University Hospitals and two large general hospitals in Amsterdam, the Netherlands. We included all HCV genotype 4 patients treated with SOF plus SMV with or without RBV initiating treatment from January until August 2015 (treatment-naïve and interferon treatment-experienced patients with advanced fibrosis or compensated liver cirrhosis (FibroScan ≥ 9.5 kPa or liver biopsy fitting with fibrosis score). All patients were treated with a combination of SOF (400 mg orally once daily) and SMV (150 mg orally once daily) with or without RBV at the physician’s discretion (weight-based upon body weight: < 80 kg 1000 mg per day; ≥ 80 kg 1200 mg per day, split in two doses daily) for 12 weeks.

Sustained viral response was defined as undetectable HCV-RNA 12 weeks after end of treatment. Rapid virological response (RVR) at Week 4 after start of treatment was documented. Different clinical (sex, age, treatment experience, medical history, co-medication, fibroscan results) and laboratory parameters (haematology, chemistry, hemostasis, virology) were documented during and after treatment: at Baseline (BL), Week 4 (W4), Week 12 (end of treatment, EOT) and 12 Weeks after EOT (end of follow-up, EFU). Liver cirrhosis was defined as FibroScan ≥ 14.0 kPa or liver biopsy fitting with liver cirrhosis (Ishak score ≥ 5 or METAVIR score F4).
**HCV-RNA measurement**

HCV-RNA was quantitatively measured using the Roche Cobas Ampliprep-Cobas Taqman (lower limit of detection 5 IU/mL; Hoffman-LaRoche, Basel, Switzerland)\(^{19}\) or the Abott RealTime HCV assay (lower limit of detection 12 IU/mL; Abbott Diagnostics, Lake Forest, IL, USA).\(^{20}\)

**Assessment of treatment outcome**

The following definitions were used to categorise treatment outcomes:

- **SVR**: Undetectable HCV-RNA 12 weeks after EOT;
- **RVR**: Undetectable HCV-RNA at Week 4 during treatment;
- **Virological Relapse**: Undetectable HCV-RNA at end of treatment but detectable HCV-RNA at Week 12 after EOT;
- **Non-SVR**: All patients who did not achieve SVR.

**Statistical analysis**

Graphic representation was performed using Graphpad Prism\textsuperscript{®} version 6 for Windows (GraphPad Software, San Diego, California, USA) and SPSS version 22 for Windows (SPSS Inc., Chicago, Illinois, USA). We used the Student’s \(t\)-test, the Mann-Whitney \(U\)-test, chi-square and Fisher’s Exact test where appropriate. Differences were considered statistically significant when \(p < 0.05\).

**RESULTS**

A total of 53 HCV genotype 4 patients initiated treatment with SOF/SMV. All patients were treated for 12 weeks. Table 1. shows the baseline characteristics of all treated patients.

Forty-one (77\%) were treated without RBV and 12 (23\%) with RBV. Of the 53 included patients, 49 achieved SVR (92\%). The four failures all had a virological relapse and did not receive ribavirin. Three out of the four failures were non-responder to previous interferon-based therapy, and one was treatment-naive. Three out of 4 failures were cirrhotic patients, of which one had severe thrombocytopenia (<90 × 10\(^E9\)/L) as a sign of portal hypertension. Figure 1. shows SVR according to cirrhosis, RBV-use, prior treatment experience and thrombocytopenia.

All patients with cirrhosis had Child-Pugh score A. There was no relationship between HCV-RNA at week 4 and non-SVR. Diabetes Mellitus Type 2, hypertension and dyslipidemia were frequent comorbidities. The use of co-medication was frequent (mainly consisted of statins, antidiabetics, and antihypertensive medication), but none of the patients used co-medication known to interact with SOF or SMV. Of the four patients with virological relapse, one patient used citalopram for depression, two patients used an ACE inhibitor for hypertension, one patient used pantoprazole and one patient used no co-medication. In the group treated with RBV, relatively more patients had thrombocytopenia (<90 × 10\(^E9\)/L) and were treatment experienced compared to the group treated without RBV prior to the initiation of treatment. Table 2. shows characteristics of the patients according to the addition of RBV to the treatment regimen.
Table 1. Baseline characteristics of patients treated with SOF and SMV +/- RBV according to SVR.

<table>
<thead>
<tr>
<th></th>
<th>SVR</th>
<th>Non-SVR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>49 (92%)</td>
<td>4 (8%)</td>
<td></td>
</tr>
<tr>
<td>Male/female (N)</td>
<td>46/3</td>
<td>4/0</td>
<td></td>
</tr>
<tr>
<td>Age at start (years, median) (range)</td>
<td>52 (37-68)</td>
<td>50 (38–54)</td>
<td>NS</td>
</tr>
<tr>
<td>RBV +/- (N)</td>
<td>12/37</td>
<td>0/4</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline HCV-RNA (IU/mL) (mean)</td>
<td>2.37 x 10E6</td>
<td>3.61 x 10E6</td>
<td>NS</td>
</tr>
<tr>
<td>HIV co-infection (N)</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Baseline ALT (U/mL) (median) (range)</td>
<td>81 (30–500)</td>
<td>59 (45–71)</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment-experienced (N, %) *</td>
<td>34 (69%)</td>
<td>3 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Fibroscan (kPA, median) (range)</td>
<td>16.6 (9.5–66.4)</td>
<td>20.5 (11.1–28.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Cirrhosis (N) Child-Pugh Score (N, %)</td>
<td>30 (61%)</td>
<td>3 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>5</td>
<td>25 (83%)</td>
<td>2 (67%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5 (17%)</td>
<td>1 (33%)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytes &lt; 90 (10E9/L) (N, %)</td>
<td>9 (18%)</td>
<td>1 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombocytes &lt; 150 (10E9/L) (N, %)</td>
<td>23 (47%)</td>
<td>1 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>RVR (N, %)</td>
<td>28 (57%)</td>
<td>3 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Co-morbidity **</td>
<td>22 (45%)</td>
<td>3 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes Mellitus Type 2</td>
<td>11 (22%)</td>
<td>1 (25%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (18%)</td>
<td>2 (50%)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7 (14%)</td>
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<td></td>
</tr>
<tr>
<td>Decompensation of liver disease</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Treatment-experienced: earlier treatment with combination therapy with (peg)interferon and ribavirin; none of the patients were protease inhibitor (PI) experienced.

Figure 1. SVR12 in all patients, patients treated with or without RBV, patients with or without cirrhosis, treatment-experienced patients and patients with thrombocyte count < 90 x10E9/L. Abbreviations: TE: Treatment-experienced defined as earlier treatment with either classical interferon alone, or combination therapy with (peg)interferon and ribavirin; T < 90: Thrombocyte count < 90 x10E9/L.
In real-life 92% of HCV genotype 4 patients with advanced fibrosis/compensated cirrhosis treated with SMV and SOF for 12 weeks achieved SVR. Real-life data on treatment with SMV and SOF in HCV genotype 4 patients are limited. Our data confirm that treatment with a combination of SMV and SOF for 12 weeks is a good option in HCV genotype 4 patients with advanced fibrosis or compensated cirrhosis. In our cohort the four patients with virological failure did not receive RBV. Three of four failures were non-responders to previous interferon-based therapy, and three of four were cirrhotic patients. Although the number of failures was very low, the addition of RBV could be considered in patients with cirrhosis and non-response to previous interferon-based therapy. Earlier studies in HCV genotype 1 patients to assess treatment success of a 12-week treatment regimen of SMV and SOF showed SVR-rates of 83–86% in patients with advanced fibrosis/compensated cirrhosis.\textsuperscript{4,14} Recently, a real-world study showed similar SVR rates in HCV genotype 1 patients with cirrhosis treated with 12 weeks of SMV and SOF and no additional effectiveness of RBV.\textsuperscript{15} Whether the addition of RBV in cirrhotic patients leads to a higher SVR-rate in genotype 4 patients is not known. In our study cohort, all 12 patients who were treated with SMV, SOF and RBV achieved SVR whereas the four patients with a viral relapse did not receive RBV. Although this difference was not statistically significant, there might be a place for the use of RBV in treatment-experienced HCV genotype 4 patients with advanced fibrosis/cirrhosis. Findings from a recent study in cirrhotic genotype 1 CHC patients treated with SOF/SMV,
showed a lower SVR-rate of 79% in treatment-experienced patients compared to 88% in treatment-naïve patients.\textsuperscript{15} There were no differences in comorbidity and co-medication between the patients with and without SVR. Whether adherence to therapy may have been a factor remains the question, as we did not assess compliance in our study. A difference in SVR-rates between patients with HCV/HIV co-infection and patients with HCV mono-infection with genotype 4 could not be assessed in our study cohort as only a small number of patients (n = 4) had an HCV/HIV co-infection, of which all achieved SVR.

Limitations of our study are the relatively small number of included patients and the fact that the use of RBV was not randomised. As the addition of RBV was determined according to the discretion of the physician, there may be a bias towards RBV-use in more severe cirrhotic patients and/or treatment-experienced patients. As a result, a reliable comparison between SVR-rates in patients treated with or without RBV cannot be made.

Although there are currently more all-oral treatment options with DAA’s available for genotype 4 HCV-infection (such as ledipasvir/sofosbuvir, daclatasvir/sofosbuvir or paritaprevir/ombitasvir/ritonavir/ribavirin), it is worthwhile to have the combination of SMV and SOF (+/- RBV) as an efficacious treatment option. In various countries, not all of the mentioned combinations are registered or available and pricing upon which treatment regimen choices are made might differ.

In conclusion, in our real-life cohort we showed that combination therapy for 12 weeks with SMV and SOF in patients with HCV genotype 4 infection and advanced fibrosis/compensated cirrhosis was an effective regimen, with an overall SVR-rate of 92%. The effectiveness of adding RBV was unclear, but could be considered, as is recommended in recent AASLD and EASL guidelines for treatment-experienced and advanced cirrhosis patients.
REFERENCES


