Research Article

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Viral Hepatitis

Clinical value of on-treatment HCV RNA levels during different sofosbuvir-based antiviral regimens

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Background & Aims: The European Association for the Study of the Liver (EASL) guidelines recommend HCV RNA measurements at specific time points during sofosbuvir(SOF)-therapy. However, it remains unclear, how these results should be interpreted. We aimed to analyze whether on-treatment HCV RNA levels predict relapse comparing the CobasAmpliPrep/CobasTaqMan v2.0 (CAP/CTM) and Abbott RealTi*m*e HCV (ART) assays.

Methods: Samples were collected from 298 patients (HCV genotypes; GT1-5) at weeks (w) 0, 1, 2, 4, 8, 12, 16, 20 and 24 during SOF-based therapy at two university clinics and tested for HCV RNA level by CAP/CTM and ART. Patients were treated with SOF/ribavirin (RBV) 12/24 w (n = 99), pegylated-interferon-alfa (PegIFN)/SOF/RBV 12 w (n = 51), SOF/simeprevir (SMV) ± RBV 12 w (n = 69) or SOF/daclatasvir ± RBV 12/24 w (n = 79).

Results: HCV RNA levels during the first 4 weeks of SOF/RBV therapy were significantly lower in GT3 patients who achieved SVR compared with those who relapsed. All GT3 patients with a week 2 result <45 IU/ml by CAP/CTM achieved SVR but only 33% of those with ⩾45 IU/ml ($p = 0.0003$). Similar results were documented with ART and 60 IU/ml as cut-off (SVR: 100% *vs.* 29%; $p = 0.0002$). In contrast, HCV RNA levels during early treatment phases were not significantly related to relapse in patients treated with other SOF-based regimens.

Residual HCV RNA was frequently detected by ART at later stages of therapy. However, SVR rates remained high in these patients. At the end of SOF/SMV ± RBV therapy HCV RNA was detectable with ART in 20% of patients, of whom 92% achieved SVR.

Conclusions: HCV RNA levels assessed at week 2 of SOF/RBV therapy can predict relapse in GT3-patients. Detectable HCV RNA results at later stages during SOF-based therapy may occur frequently with the more sensitive ART. However, this should not lead to treatment extension.

Lay summary: We analyzed the predictive value of hepatitis C virus (HCV) RNA levels measured at different time points for treatment efficacy. We found that the level of HCV RNA measured at week 2 of antiviral therapy can be used to predict treatment success in patients with HCV genotype 3 infection treated with sofosbuvir and ribavirin but not in patients treated with other sofosbuvir-based regimens. Low level HCV RNA is frequently detected by the RealTime HCV assay during later stages of antiviral therapy. However, this is not associated with reoccurrence of HCV RNA after the end of treatment.

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Keywords: Hepatitis C; Relapse; Sustained virological response; Relapse; HCV RNA; HCV RNA assays; HCV RNA quantification; Direct-acting antivirals; Response predictors; HCV RNA kinetics; Sofosbuvir.

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Abbreviations: SOF, sofosbuvir; CAP/CTM, COBAS AmpliPrep/COBAS TaqMan v2.0; ART, Abbott RealTi*m*e HCV test; GT, genotype; RBV, ribavirin; PegIFN, pegylated-interferon alfa; SMV, simeprevir; HCV, hepatitis C virus; SVR, sustained virological response; DAA, direct-acting antivirals; PI, protease inhibitor; w, weeks; LOQ, lower limit of quantification; LOD, lower limit of detection; LDV, ledipasvir; TND, target not detected; DCV, daclatasvir.

Introduction

Chronic hepatitis C virus (HCV) infection is an important cause of liver cirrhosis and hepatocellular carcinoma [1,2]. For almost ten years, standard treatment of chronic HCV infection had been dual therapy consisting of pegylated-interferon alfa (PegIFN) and ribavirin (RBV) [3]. Today, PegIFN/RBV is still the standard of care in many parts of the world [4]. Given the relatively low rates of sustained virological response (SVR) in certain patient groups

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and the significant adverse effects associated with this regimen, response predictors were of high relevance [5,6]. On-treatment quantitative HCV RNA levels at certain time points during therapy were shown to be closely related to the treatment outcome and were soon established as a major parameter to determine treatment duration and futility [7]. Over the recent years, major advances have been made in treating HCV through the development of direct-acting antivirals (DAA). Using the first generation of these new drugs, the protease inhibitors (PI) telaprevir and boceprevir, treatment duration and stopping rules were still dependent on HCV RNA levels due to their high predictive value for SVR [8,9]. In 2013, the nucleotide analogue NS5B polymerase inhibitor sofosbuvir (SOF) was approved in the US and shortly afterwards in several European countries. The major advantage of SOF compared to other DAAs besides its pangenotypic activity is its very high barrier to resistance resulting in a lack of virological breakthroughs during treatment [10]. The combination of SOF with RBV and/or a second DAA has made an interferon-free HCV therapy reality [11,12]. Currently, there are several highly efficient IFN-free treatment options available. Due to the good tolerability and lack of virological breakthrough no response-guided regimen has been explored so far [13]. According to the prescribing information, all patients are treated for a fixed duration without the need for on-treatment HCV RNA measurements. Overall, efficacy of SOF-based therapies is high [11,12]. However, there is a certain proportion of patients who experience treatment failure due to virological relapse. At present, the European Association for the Study of the Liver (EASL) guidelines recommend monitoring of quantitative HCV RNA at weeks 2 and 4 of SOF-based therapy as well as at the end of treatment to ensure treatment efficacy and patient compliance [2]. In clinical routine, HCV RNA measurements may be performed even more often, at several time points during therapy using different HCV RNA assays. Until recently, there have been limited data available on how on-treatment HCV RNA results during SOF-based regimens need to be interpreted and whether there is any association with the final treatment outcome.

Here we aimed to analyze whether HCV RNA levels during different approved SOF-based therapies predict the final treatment outcome comparing the two most widely used HCV RNA assays: the COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0 (CAP/CTM) and the Abbott RealTi*m*e HCV test (ART).

Patients and methods

Patient samples and treatment regimens

Overall, 298 HCV-mono-infected patients (genotype; GT1-5) were included. Patients were treated with one of the following regimens:

1. SOF + RBV for 24 weeks: n = 67 patients infected with HCV GT1, 3 or 4
2. SOF + RBV for 12 weeks: n = 32 patients infected with HCV GT2
3. PegIFN + RBV + SOF for 12 weeks: n = 51 patients infected with HCV GT1-5
4. SOF + SMV ± RBV for 12 weeks: n = 69 patients infected with HCV GT1
5. SOF + DCV ± RBV for 12 or 24 weeks: n = 79 patients infected with HCV GT1 or 3

(SMV, simeprevir; DCV, daclatasvir)

Samples were collected at weeks (w) 0, 1, 2, 4, 8, 12 (for all regimens), at w 16 and 20 (for SOF/RBV 24-weeks) as well as at w 24 (for all 24 w regimens) of SOF-based treatments at two German university clinics (Frankfurt, Hanover).

HCV RNA measurements

All available samples were tested for HCV RNA level by the COBAS® AmpliPrep®/ COBAS® TaqMan® HCV Test, v2.0 (CAP/CTM) and the Abbott RealTi*m*e HCV test® (ART). Testing was performed at Frankfurt University and Hannover Medical School according to the manufacturers' instructions. Performance characteristics of the two assays have been described in detail previously [14,15]. Samples, in which a valid test result was not available for both assays, were withdrawn from analysis. The lower limit of quantification (LOQ) and the limit of detection (LOD) of the CAP/CTM is 15 IU/ml. For the ART the LOQ and LOD is 12 IU/ml.

Diagnosis of cirrhosis

Diagnosis of cirrhosis was based on either liver biopsy or non-invasive imaging. In the majority of cases this was performed by transient elastography (FibroScan, Echosens, Paris, France) using a cut-off of 12.5 kPa [16]. Diagnosis of cirrhosis by other imaging methods included ultrasound, magnetic resonance imaging or a combination of the two. Here, the diagnosis was established based on typical imaging findings, including liver surface nodularity, liver segment I hypertrophy, splenomegaly, hepatofugal portal venous flow, enlargement and tortuosity of the hepatic artery and portosystemic vascular shunts [17].

Treatment outcomes

SVR was defined as undetectable HCV RNA 12 weeks after the end of antiviral treatment (SVR12) in line with current guideline definitions [2]. SVR12 was assessed using the CAP/CTM. In thirteen patients (4%) who were lost to follow up only a SVR4 (n = 9) or SVR8 (n = 4) result was available. Given the high concordance between SVR12 and SVR4/8 these patients were considered as SVR patients [18]. A virological relapse was defined as recurrence of quantifiable HCV RNA after the end of therapy. Three patients were HCV RNA positive at the planned end of treatment. However, two of these had discontinued treatment shortly before this last appointment due to adverse effects. For the third patient an earlier treatment discontinuation due to poor treatment tolerability was suspected. Therefore, all three patients were considered to be relapsers.

Statistics

Microsoft Excel (Microsoft, Redmond, Washington, USA) was used for data collection and GraphPad Prism for Mac (version 6.0; GraphPad Software Inc., La Jolla, California, USA) for analyzing the data. For statistical analysis an undetectable HCV RNA result was calculated as 0 or as 1 if logarithmic values were used. Detectable test results below the limit of quantitation (LOQ) were calculated as 15 (CAP/CTM) or 12 (ART). Categorical data were compared with the Fisher's exact test or, if more than two parameters were analyzed, with the Chi-square test. Continuous data were analyzed with the Mann-Whitney *U* test. Receiver operating characteristic (ROC) curves were generated to identify optimal cut-offs. p values of <0.05 were considered as statistically significant.

Ethics

This study was performed according to the declaration of Helsinki. The retrospective, anonymous retesting of patient samples, and the anonymous analyzing of patient data was approved by the ethical committee of Hannover medical school.

Results

Baseline patient characteristics and treatment outcomes

Overall, 298 patients were included at the two study sites. Baseline characteristics of the whole study population are shown in Table 1A.

In total 99 patients were treated with SOF/RBV dual therapy. Treatment with SOF/RBV for 24 weeks achieved SVR in 52% (n = 16/31), 64% (n = 21/33) and 67% (n = 2/3) of HCV GT1, GT3 and GT4 infected patients, respectively. HCV GT2 patients were treated with SOF/RBV for only 12 weeks and 88% (n = 28/32)

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