Clinical studies on hepatitis B, C, and E virus infection

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Citation for published version (APA):
CHAPTER 6

The Observed Effect of Gastric Bypass Surgery on the Treatment of Chronic Hepatitis C Virus (HCV) Infection; A Case Report

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In press Annals of Hepatology 2017
ABSTRACT

Chronic hepatitis C virus (HCV) infection can be cured with treatment using direct-acting antivirals (DAAs). Although these drugs have been widely studied, information about certain special populations are missing. In this case report we describe a treatment-experienced patient with chronic HCV infection genotype 1b, treated with 150mg/day simeprevir, 400mg/day sofosbuvir, and 1000mg/day ribavirin for 24 Weeks, after a Roux-and-Y gastric bypass. At steady-state a pharmacokinetic curve was recorded of sofosbuvir, GS-331007, and simeprevir. Ribavirin trough plasma concentration (C_{trough}) was determined.

The simeprevir area under the time curve (AUC_{last}) and C_{trough} were 9.42 h mg/L and 0.046mg/L, respectively. Compared to what was described in the literature, simeprevir exposure was low and therefore the simeprevir dose was increased to 300mg/day. The increased dose of simeprevir was well tolerated and C_{trough} was 0.532mg/L. Sofosbuvir AUC_{last} and C_{trough} were 0.63 h mg/L and 0.0013mg/L. GS-331007 AUC_{last} and C_{trough} were 21.02 h mg/L and 0.35mg/L. Ribavirin C_{trough} was 2.5mg/L. Sofosbuvir, GS-331007, and ribavirin exposure were comparable with levels described in literature. The patient achieved a sustained virologic response twelve weeks after the completion of treatment.
INTRODUCTION

Direct-acting antivirals (DAAs) are highly effective for the treatment of chronic hepatitis C virus (HCV) infection. Simeprevir is a second generation protease inhibitor (PI) which is a highly active DAA, especially in combination with sofosbuvir for the treatment of HCV-infection genotype 1 and 4. The relatively new DAAs have been widely studied but information about certain special populations is often not known. We are the first to describe a patient who underwent bariatric surgery and who, after relapsing to previous DAA therapy, was successfully treated for HCV-infection genotype 1b with sofosbuvir (Sovaldi®, Gilead Sciences, Cambridge, United Kingdom) simeprevir (Olysio®, Janssen-Cilag International, Beerse, Belgium), and ribavirin.

CASE REPORT

We describe a 61-year old Brazilian female patient, who presented to our outpatient clinic in 2011 with chronic HCV genotype 1b infection. She was diagnosed with HCV-infection in 2008, but the transmission route was unknown. Possible sources of infection included dental treatment or a caesarean section in Brazil.

The patient was severely obese with a body mass index (BMI) of 35.4 kg/m² (weight 84 kg, height 1.54 m). Ultrasound demonstrated hepatic steatosis without any ultrasonographic signs of cirrhosis. Evaluation of liver stiffness using Fibroscan® showed a value of 13.6 kPa, consistent with META VIR fibrosis score F3 (severe fibrosis). A liver biopsy showed moderately active periportal inflammation and moderate periportal fibrosis with formation of septae in less than 50% of portal fields (META VIR score A2/F2-3) and macrovesicular steatosis in 40–50% of hepatocytes with minimal pericellular fibrosis (Brunt score steatosis grade 2, fibrosis stage F1). Laboratory testing showed mildly elevated liver enzymes with an ALT of 77 U/L, AST of 51 U/L and gamma-GT of 57 U/L. Serum bilirubin, prothrombin time, albumin, creatinine, thrombocytes, and fasting blood glucose values were all normal. HCV RNA was \(9.56 \times 10^5\) IU/mL and HBsAg and anti-HIV 1 & 2 antibodies were negative.

The patient was a non-responder to treatment with peginterferon-alpha and ribavirin in 2009. In 2013, she was included in a clinical trial and was treated with DAAs daclatasvir and asunaprevir for 24 weeks. A relapse occurred after this treatment.

Whilst waiting for registration and reimbursement of the first DAAs in the Netherlands the patient decided to undergo gastric bypass surgery in 2014 (Roux-and-Y gastric bypass). She came back to our outpatient clinic in 2015 for (re-)treatment of the chronic HCV-infection. Her weight had reduced to 59 kg (BMI 24.9 kg/m²), and transaminases had improved (ALT 48 U/L; AST 39 U/L). All other liver enzymes and liver function tests were not altered and HCV RNA load was \(5.64 \times 10^6\) IU/mL. Sequencing of the viral genome was performed on the regions NS5A and NS3 (as she had received a NS5A inhibitor and a PI), which showed a high level of resistance associated substitutions (RAS) to NS5A inhibitors on the loci L31M/I and Y93H. There were no RAS present in the NS3 gene of the viral genome. For these reasons, we decided to treat the patient with 400mg sofosbuvir once daily, 150mg simeprevir once daily and 1000 ribavirin per day, for a total of 24 weeks.
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Figure 1. Plasma concentrations of 400mg sofosbuvir and GS-331007 (A) and 150 and 300mg simeprevir (B).

A: Sofosbuvir concentrations at Week 3: C_{trough}: 0.001 mg/L; C_{max}: 0.35 mg/L; T_{max}: 2.25h; AUC_{0-24}: 0.63 h*mg/L; T_{1/2}: 0.5h. GS-331007: C_{trough}: 0.35 mg/L; C_{max}: 1.55 mg/L; T_{max}: 4.91h; AUC_{0-24}: 21.02 h*mg/L; T_{1/2}: 10.3h. Sofosbuvir reference values (400 mg once daily treatment-naïve HCV genotype 1-infected subjects without cirrhosis). Sofosbuvir: T_{max}: 0.5-1.5h; C_{max}: 0.55mg/L; AUC_{0-24}: 1.03 h*mg/L. GS-331007: T_{max}: 2-4h; C_{max}: 582 mg/L; AUC_{0-24}: 7.12 h*mg/L.

B: Simeprevir concentrations at Week 3: C_{trough}: 0.046 mg/L; C_{max}: 1.20 mg/L; T_{max}: 3.25h; AUC_{0-24}: 9.41 mg/L; T_{1/2}: 4.6h. Week 14: C_{trough}: 0.532 mg/L. Simeprevir reference values (treatment experienced patients 150mg, once daily): C_{trough}: 1.41 mg/L; C_{max}: 4.38 mg/L; T_{max}: 2.03-9.87h; AUC_{0-24}: 57.4 h*mg/L.
The effect of gastric bypass surgery on the absorption of the DAAs is unknown. Simeprevir and ribavirin in particular must be taken with food for adequate plasma concentrations. However, due to the bariatric surgery, the patient was not able to eat large meals. To study the exposure of the DAAs and ribavirin in this patient, a pharmacokinetic curve was obtained at Week 3 of DAA treatment. Blood was sampled at \( t = 0 \) (pre-dose), 2, 3, 5, 6, 8, and 24 hours after intake of the DAAs. DAA plasma concentrations were determined using an in-house made, validated HPLC-MS/MS tandem mass spectrometry assay and used to calculate pharmacokinetic parameters. The assay lower limits of quantification for sofosbuvir, GS-331007 and daclatasvir were 2.5ng/mL, 10ng/mL, and 10 ng/L respectively. The precision for low, medium and high quality control (QCs) samples was <10 % for all analytes. Ribavirin plasma concentrations were determined using validated HPLC assay with UV detection.

At Week 3, the area under the time curve (AUC\(_{\text{last}}\)) for sofosbuvir was 0.63 h.mg/L, the maximum plasma concentration (C\(_{\text{max}}\)) was 0.35 mg/L, and the minimum plasma concentration (C\(_{\text{trough}}\)) was 0.0013 mg/L. For the main inactive metabolite of sofosbuvir, GS-331007, the AUC\(_{0-24}\) was 21.02 h.mg/L, C\(_{\text{max}}\) was 1.55 mg/L, and the C\(_{\text{trough}}\) was 0.35 mg/L (Figure 1a).

For simeprevir, at Week 3 of treatment, the AUC\(_{0-24}\) was 9.42 h.mg/L, the C\(_{\text{max}}\) was 1.21 mg/L, and the C\(_{\text{trough}}\) was 0.046 mg/L (Figure 1b). Ribavirin concentration was 2.5mg/L. Sofosbuvir and ribavirin concentrations were considered adequate but simeprevir concentrations were sub-therapeutic compared with those described in literature.

As a result, at Week 10 of treatment, the simeprevir dose was doubled to 150 mg twice daily (taken together with food). At Week 14 the trough concentrations of ribavirin and simeprevir were determined again and the C\(_{\text{trough}}\) of simeprevir and ribavirin were 0.532mg/L and 3.5mg/L, respectively. The haemoglobin level had dropped from 12.3 g/dL to 9.8 g/dL. HCV RNA was undetectable during treatment at Week 3, 4, 12, 24 (end of treatment) and 12 weeks after end of treatment (sustained virologic response, SVR12).

During treatment, the main side effect was extreme fatigue. Liver enzymes, liver function tests and renal function were all normal during treatment.

For this case report no formal ethical approval was obtained as all procedures were performed for regular health care purposes. The patient did not have to comply to certain extra examinations of life style rules. However, the patient gave consent for performing the pharmacokinetic curve and publication of this paper. This was recorded in the patient chart.

**DISCUSSION**

We are the first to describe a patient who was successfully treated with DAAs including an adjusted dose of simeprevir after undergoing gastric bypass surgery. Although simeprevir was not deemed to be ideal in this patient, given the food-dependent uptake, there was no alternative choice due to existing resistance to NS5A inhibitors.

The goal of bariatric surgery is to decrease the intake of food and absorption of nutrients for severely obese patients, resulting in weight loss. These surgeries also affect drug absorption of orally administered drugs, as the gastrointestinal (GI) tract is substantially altered. Little is known about the effects of a Roux-and-Y gastric bypass on drug exposure.
On one hand, gastric pH rises which could cause increased absorption. On the other hand, absorption could decrease, as the transit time of a drug through the GI tract is reduced.\textsuperscript{16}

We treated the patient for 24 weeks, according to national and international guidelines, as she relapsed to earlier dual NS3/NS5A DAA therapy.\textsuperscript{8-10} We also tried to enhance the potency of the treatment by adding ribavirin (at a weight-based dose). Simeprevir and ribavirin are both recommended to be taken with food, as food intake increases the absorption of both drugs.\textsuperscript{11,17} According to the simeprevir label, the AUC increases by approximately 60\% when administered with a fatty meal or normal breakfast.\textsuperscript{11} In this case, Simeprevir $C_{\text{trough}}$ levels were 97\% lower than comparable reference values, and the $\text{AUC}_{0-24}$ was 84\% lower. Our patient was not able to have large or “normal sized” meals (i.e. a high intake of calories) anymore and we postulate that this resulted in the extremely low exposure to simeprevir. Despite the fact that HCV RNA was undetectable, we doubled the dose of simeprevir to increase the plasma exposure and efficacy. This dose was well-tolerated and the $C_{\text{trough}}$ Plasma concentration at Week 14, (4 Weeks after doubling the dose), was approximately 11-fold higher than the Week 3 $C_{\text{trough}}$ level (62\% lower than the reference value). This extreme increase is the result of the non-linear pharmacokinetics of simeprevir.

For ribavirin, we strived to attain a plasma concentration of 2.0-3.0 mg/L at steady-state.\textsuperscript{18} At Week 3 of treatment the plasma concentration was already 2.5 mg/L, which is remarkable as the patient had a low intake of food.\textsuperscript{17} These high ribavirin levels caused anaemia and the patient suffered from extreme fatigue. It was considered to lower the dose of ribavirin, but because the haemoglobin levels remained stable throughout the whole course of treatment and the patient did not want a dose reduction, the starting dose of 1000mg/day was continued. The high plasma concentrations of ribavirin (compared to the low levels of simeprevir) could also be related to the low body weight of < 60 kg of the patient after gastric bypass surgery. The fact that a large or “normal” meal could not be consumed seems less important for an adequate ribavirin level as the initial dose was already relatively high.

Sofosbuvir pharmacokinetics were not affected by the gastric bypass or the low intake of food as the exposure to both sofosbuvir and GS-331007 (the main inactive metabolite of sofosbuvir) were sufficient. This was as expected because it was earlier described that a high-fat meal does not influence the plasma concentration of sofosbuvir or GS-331007.\textsuperscript{19}

This case report describes a patient with chronic HCV-infection genotype 1b without liver cirrhosis, but with a relapse after earlier dual DAA-treatment, who was successfully treated with simeprevir, sofosbuvir, and ribavirin for 24 weeks after undergoing gastric bypass surgery. Adequate sofosbuvir and ribavirin plasma concentrations were achieved, however, simeprevir plasma concentrations were low when simeprevir was dosed according to the drug label (150 mg once daily).\textsuperscript{11} Both bariatric surgery and low intake of food can influence drug absorption and drug exposure. Awareness is needed when patients who underwent bariatric surgery are treated with certain drugs without any experience in this specific condition. This is especially the case for simeprevir, as absorption is dependent of food intake, it has non-linear pharmacokinetics and possibly more severe side effects when given in high doses. Patients with a history of bariatric surgery who are treated with simeprevir should be closely monitored using, for example, therapeutic drug monitoring.
ACKNOWLEDGEMENTS

We thank the patient for participating. Secondly we would like to thank the laboratory personnel at the Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom and the laboratory personnel at the Clinical Pharmacy of Radboud university medical center, Nijmegen. We also thank the nurses and pharmacy personnel Academic Medical Center, Amsterdam, the Netherlands, for their support during the hospital admission of the patient. We thank Yuma Bijleveld for her support during the hospital admission.
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