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Short Communication

Decreased tacrolimus plasma concentrations during HCV therapy: a drug–drug interaction or is there an alternative explanation?

E.J. Smolders [a,*], S. Pape [b], C.T.M.M. de Kanter [c], A.P. van den Berg [d], J.P.H. Drenth [b], D.M. Burger [a]

[a] Department of Pharmacy, radboud university medical center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands
[b] Department of Gastroenterology and Hepatology, radboud university medical center, Nijmegen, The Netherlands
[c] Department of Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands
[d] Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands

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ABSTRACT

Chronic hepatitis C virus (HCV) infection can cause severe liver cirrhosis, for which liver transplantation is the only therapy. To prevent organ rejection, transplanted patients are treated with immunosuppressive agents. We describe two transplanted patients treated with tacrolimus who were simultaneously treated with direct-acting antivirals (DAAs) for their chronic HCV infection. No pharmacokinetic drug–drug interactions (DDIs) were expected between tacrolimus and the selected DAAs. However, in both patients, tacrolimus plasma concentrations decreased during HCV treatment. We hypothesise that decreased plasma concentrations were not caused by a DDI but were an indirect result of the clearance of the HCV infection. During chronic HCV infection, pro-inflammatory cytokines may inhibit cytochrome P450 (CYP) enzymes, which are primarily responsible for tacrolimus metabolism. If this is true, then with clearance of the virus the activity of these enzymes will normalise and tacrolimus metabolism will increase. These changes were clinically relevant because the tacrolimus dosage needed to be adjusted. Therefore, physicians should be aware that CYP substrates with narrow therapeutic ranges might require dose adaption during HCV therapy with DAAs.

1. Introduction

Chronic hepatitis C virus (HCV) infection can lead to cirrhosis and eventually cause end-stage liver disease. This is a situation where liver transplantation is the only remaining therapy. Twenty-five percent of all liver transplantations are due to HCV-induced cirrhosis [1]. To prevent organ rejection following liver transplantation, patients are treated with immunosuppressive agents such as tacrolimus, cyclosporine and mycophenolic acid.

Direct-acting antivirals (DAAs) have entered the current Dutch guidelines for HCV treatment (http://www.hcvrichtsnoer.nl/). DAAs are extensively metabolised by drug-metabolising enzymes, making them potential victims of drug–drug interactions (DDIs). In addition, DAAs may induce or inhibit drug-metabolising enzymes directly. This makes them potential perpetrators of DDIs. Possible DDIs between DAAs and immunosuppressive agents are the subject of studies prior to market access, since it is likely that these two drugs will be used concomitantly. For example, we know that DDIs are absent between the DAAs daclatasvir and sofosbuvir and the immunosuppressive agents tacrolimus and mycophenolic acid [2]. By contrast, tacrolimus interacts with simeprevir, necessitating therapeutic drug monitoring (TDM) of tacrolimus [2].

In this paper, we describe two cases of patients who underwent liver transplantation and who used tacrolimus simultaneously with daclatasvir, sofosbuvir and ribavirin. There were no DDIs; however, unexpectedly decreased tacrolimus plasma concentrations were reported.

2. Case reports

2.1. Patient 1

Patient 1 was a 56-year-old male with chronic HCV genotype 3 infection. He was diagnosed in 2009 and had received prior treatment with pegylated interferon (peg-IFN) and ribavirin but failed to respond (2010 and 2011). He rapidly progressed to cirrhosis and end-stage liver disease, resulting in liver transplantation in 2012. He received 2 mg/day tacrolimus and 500 mg mycophenolic acid twice daily (b.i.d.) (target value, 2–3 μg/L). These doses had been stable since August 2013. In 2015, he was re-treated for his HCV infection with 400 mg/day sofosbuvir and 600 mg ribavirin b.i.d. for

* Corresponding author. Department of Pharmacy, radboud university medical center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands. Fax: +31 24 366 8755.
E-mail address: Elise.Smolders@radboudumc.nl (E.J. Smolders).

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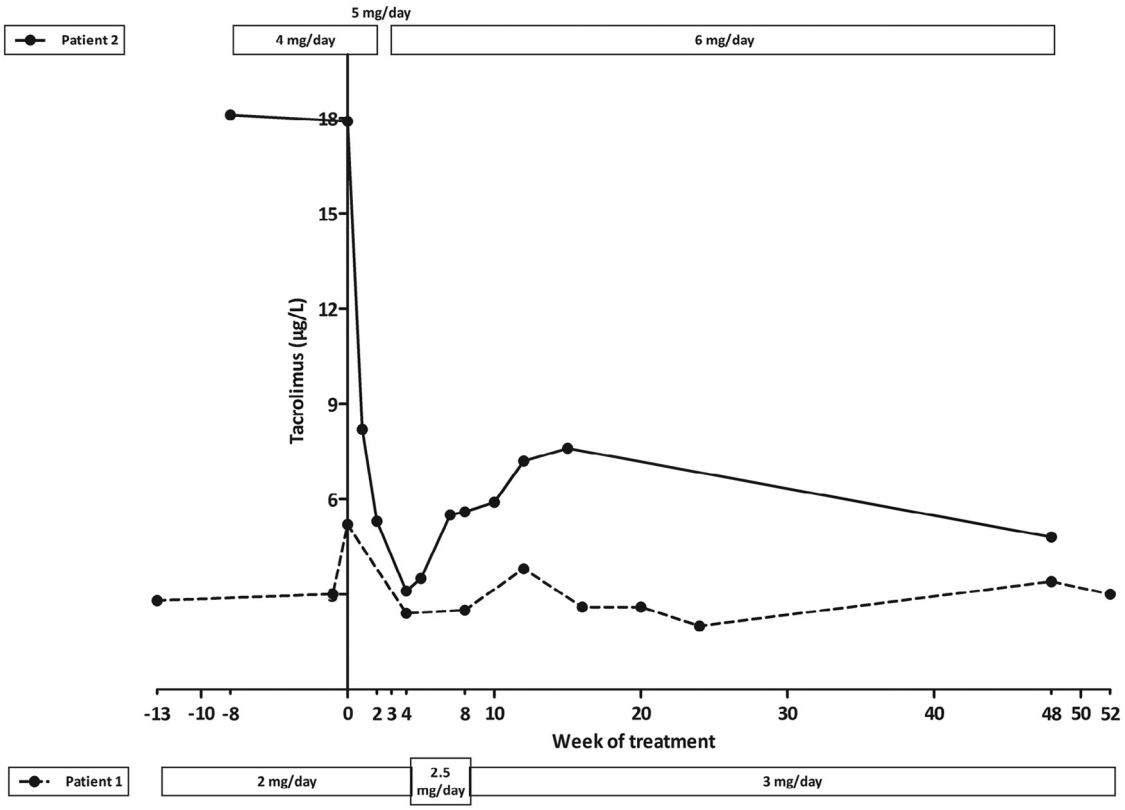

Fig. 1. Tacrolimus plasma concentrations and tacrolimus dosage during hepatitis C virus (HCV) treatment for Patients 1 and 2. The figure shows the tacrolimus plasma concentration (left *y*-axis) and the tacrolimus dosage in mg/day. The weeks of treatment are shown on the *x*-axis. Patient 1 was treated for 24 weeks (follow-up data are missing). Patient 2 was treated for 12 weeks; follow-up data are shown at Week 24 of treatment. The estimated glomerular filtration rate remained stable during treatment in both patients.

24 weeks. At the start of therapy, the tacrolimus minimum plasma concentration (C_{trough}) was 5.5 µg/L [estimated glomerular filtration rate (eGFR) = 61 mL/min], followed by a decreased C_{trough} to 2.4 µg/L at Week 4. This required an increase of tacrolimus dosage to 2.5 mg/day. At Week 8, the C_{trough} was 2.5 µg/L and the tacrolimus dosage was further elevated to 3 mg/day, resulting in an increased C_{trough} of 3.8 µg/L. The dosage was subsequently lowered to 2.5 mg/day.

The patient remained on that dosage during the rest of HCV treatment. The patient reached sustained virological response 12 weeks after completing treatment (SVR12). His tacrolimus plasma concentration has been stable since, and the patient is still treated with a dosage of 2.5 mg/day (Fig. 1).

2.2. Patient 2

Patient 2 was a 74-year-old male with a chronic HCV genotype 1b infection. He was treated twice with peg-IFN and ribavirin (2002 and 2004) and relapsed both times. Cirrhosis was diagnosed in 2008 and he developed hepatocellular carcinoma for which he received chemoembolisation and radiofrequency ablation. In June 2010, he underwent his first liver transplantation, which was complicated by a grade 2 rejection. A second liver transplantation was performed in August 2010. Since his transplantation, he has been on mycophenolic acid 1000 mg b.i.d. and tacrolimus 4 mg/day (target value, 5–10 µg/L). In May 2015, he developed mild ascites and HCV therapy was initiated (eGFR = 60 mL/min). He received sofosbuvir 400 mg/day, daclatasvir 60 mg/day and ribavirin 1000 mg/day for 12 weeks. His tacrolimus C_{trough} was 17.9 µg/L at the start of therapy and had decreased to 5.3 µg/L at Week 2 of therapy. His tacrolimus dosage was increased to 5 mg/day but at Week 4 his C_{trough} had dropped to 3.1 µg/L and the dosage was increased again to 6 mg/day. From this moment on, his tacrolimus C_{trough} rose gradually to 7.2 µg/L at the end of therapy (Fig. 1). His treatment was complicated due to anaemia (haemoglobin 6.1 g/dL) necessitating blood transfusions and temporary withdrawal of ribavirin. In November 2015, he achieved SVR12.

3. Discussion

This case report describes two liver transplant recipients receiving tacrolimus who have been treated for HCV successfully. Tacrolimus is a substrate for cytochrome P450 (CYP) 3A4 and P-glycoprotein. It has a narrow therapeutic range and pharmacokinetics show high interpatient variability requiring close TDM with dose adjustment.

At the start of treatment, no DDIs between tacrolimus, sofosbuvir, daclatasvir and ribavirin had been described. However, to maintain target tacrolimus C_{trough} plasma concentrations, we found that the tacrolimus dosage had to be increased during HCV treatment. This was an unexpected observation in view of the fact that none of the DAAs influenced CYP3A4, the main metabolising enzyme of tacrolimus.

We hypothesise that decreased tacrolimus plasma concentrations resulted from repression of drug-metabolising enzymes, such as CYP3A4, by an inflammatory/infectious stimulus. Pro-inflammatory cytokines such as interleukin 6 and tumour necrosis factor-alpha (TNFα) inhibit CYP3A4 enzymes [3,4]. This has been studied both in vitro [3,4] and in vivo and is described in infectious (human immunodeficiency virus [HIV] [5]) and inflammatory