CASE REPORT

Ribavirin-induced anaemia reduced tacrolimus level in a hepatitis C patient receiving haemodialysis

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SUMMARY

A 37-year-old man with hepatitis C virus (HCV) genotype 3A developed renal failure. In 2007, the patient received a renal transplant and started receiving tacrolimus (Tac); the transplant subsequently failed. In April 2015, the patient restarted haemodialysis and in May initiated sofosbuvir 400 mg and ribavirin 400 mg daily. Baseline Tac level was 6.6 ng/mL and haemoglobin (Hb) was 10.3 g/dL. The patient then left the country for vacation and Hb was found to be dramatically low at 3.7 g/dL on return on 5 August. Ribavirin was put on hold, while darbepoetin dose was increased. On 23 August, Tac level was found undetectable; hence, dosage was increased. Hb eventually bounced back to >10 g/dL in October and Tac to 7.2 ng/mL; ribavirin was restarted at 200 mg three times weekly. HCV RNA level was undetectable at 3 months and remained undetectable 12 weeks after therapy finished.

BACKGROUND

In 2015, daily sofosbuvir (SOF) 400 mg and weight-based ribavirin (RBV) at 1000 mg or 1200 mg for 24 weeks is an alternative regimen for treatment-naïve patients with hepatitis C virus (HCV) genotype 3 infection (regardless of cirrhosis status) as per Infectious Diseases Society of America (IDSA) guideline based on results from the VALENCE study (SOF and RBV in Treatment-Naïve and Treatment-Experienced Subjects With Chronic Genotype 2 or 3 HCV Infection).¹ In Canada, where daclatasvir is not available, SOF/RBV for 24 weeks is the recommended therapy for treatment naïve (both cirrhotic and non-cirrhotic) and non-cirrhotic treatment-experienced patients with HCV genotype 3 infection.² However, in the VALENCE study, patients with creatinine clearance <60 mL/min were excluded. There was no specific recommendation for HCV genotype 3 treatment in individuals on haemodialysis (HD).

CASE PRESENTATION

A 37-year-old South Asian male was infected with HCV genotype 3A. He first presented with hypertension and proteinuria secondary to IgA nephropathy in 2001 and later developed end-stage renal disease. After 2 years of peritoneal dialysis, the patient began HD in 2003. HCV infection was newly diagnosed in 2006 after the patient returned from receiving HD in India during his vacation. He never received any peginterferon (PEG)/ribavirin (RBV) treatment initially due to cost concerns. Also, nephrologist at that time suggested the HCV infection to be managed

after his kidney transplant (no evidence of cirrhosis). In 2007, the patient received a renal transplant in India which subsequently failed due to recurrent IgA nephropathy and de novo membranoproliferative glomerulonephritis (immune complex-mediated type) likely secondary to his HCV infection.

TREATMENT

Since renal transplantation, the patient has been maintained on tacrolimus (Tac), mycophenolate mofetil and prednisone while awaiting to go back on the transplant list in Canada. On 15 April 2015, the patient started receiving HD again and initiated combination HCV therapy of SOF 400 mg and RBV 400 mg daily on 29 May 2015. The patient's initial HCV RNA was 6 808 975 IU/mL on 30 September 2014 and had dropped to 90 281 IU/mL on 29 May 2015 (at initiation of SOF/RBV).

OUTCOME AND FOLLOW-UP

The patient's whole-blood Tac level was 6.6 ng/mL (target 4–6) at dosage of 1 mg twice daily on 13 June; haemoglobin (Hb) level was 10.3 g/dL (haematocrit (Hct)=0.31 L/L) on 6 July. The patient then left to USA for a 1-month vacation and his Hb was found to be dramatically low at 3.7 g/dL (Hct=0.11 L/L) on return to Canada on 5 August. RBV was immediately put on hold while darbepoetin dose was increased from 20 µg to eventually 200 µg intravenously per week. In August the patient received 5 units of packed red blood cells in total and Hb remained in the 4's; a bone marrow biopsy was performed to rule out myeloproliferative disorder but the result was unremarkable. On 19 August, Tac level was reported at 1.0 ng/mL and dropped to undetectable level 5 days later. Tac dosage was increased to 1.5 mg twice daily (yielding level=1.4 ng/mL) and then 2.5 mg twice daily. During the month of September, Hb gradually bounced back to >10 g/dL (on 2 October); RBV was restarted at 200 mg three times weekly on 5 October. On 14 October, Tac level was 7.2 ng/mL; Tac dosage was gradually cut back and maintained at 1.5 mg twice daily (with levels around 4 ng/mL). SOF/RBV was stopped on 2 December 2015. Since initiation of SOF/RBV, HCV RNA level was first tested and reported undetectable at 3 months; it remained undetectable 12 weeks after therapy finished.

DISCUSSION

RBV is a broad-spectrum antiviral agent that had shown minimal urinary excretion in patients on HD and a 4-hour HD session removed about 2.4% of the oral dose.³ Clinical trials of PEG alfa-2a

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with or without RBV in patients on HD had used a low dose of 200mg/day, which was further reduced in a stepwise fashion if Hb dropped.^{4,5} Compared with patients receiving PEG monotherapy, patients receiving PEG/RBV were more likely to have a Hb less than 8.5 g/dL and required a higher dosage of erythropoietin stimulating agents (ESA). Hb began to be significantly lower at 4 weeks and returned to baseline 12 weeks after discontinuation of RBV. In fact, patients with a more marked reduction of Hb during treatment are more likely to achieve higher sustained virologic response rates.⁶ Practitioners are always facing the dilemma of risk (anaemia) versus benefit (efficacy) in whether/how much RBV dosage should be reduced in renal impairment, especially in countries where RBV therapeutic monitoring is not accessible. Currently, American Association for the Study of Liver Diseases/IDSA guideline for treatment-naïve genotype 3 patients has changed: glecaprevir/pibrentasvir is recommended based on results from ENDURANCE-3 trial (A Study Comparing Efficacy and Safety of ABT-493/ABT-530 to SOF Dosed With Daclatasvir in Adults With HCV Genotype 3 Infection)⁷ and sofosbuvir/velpatasvir is recommended based on ASTRAL-3 trial (Comparison of SOF/Velpatasvir Fixed Dose Combination for 12 Weeks With SOF and RBV for 24 Weeks in Adults With Chronic Genotype 3 HCV Infection - in which patients with creatinine clearance <60 mL/min were excluded)⁸; SOF/RBV is no longer listed as alternative. Glecaprevir/pibrentasvir had reported safety outcomes in patients with stage 4 or stage 5 chronic kidney disease including patients on dialysis, with pruritus and fatigue the most common adverse reactions and no serious adverse reaction reported.⁹ This combination tablet was approved in Canada in 2017; there has been no update on Canadian HCV treatment guidelines published yet since 2015. In our patient, who started RBV at a reduced dosage of 400 mg daily, Hb dropped significantly 1–2 months after initiation of therapy and returned to baseline 8 weeks after RBV was put on hold. With the availability of newer direct antivirals, this case again supports the abandoning of RBV containing regimens in treatment guidelines. Interestingly, as per HCV-TARGET cohort, patients taking SOF-containing regimens with estimated glomerular filtration rate ≤45 mL/min more frequently experienced anaemia, even with RBV-free regimens (31% vs 16%).¹⁰ At this moment, glecaprevir/pibrentasvir (SOF free) appears to be the most favourable option in genotype 3-infected individuals with severe renal impairment, who are already at increased risk of anaemia. In the very unlikely instance that RBV is warranted in a patient on HD, careful monitoring of Hb should be emphasised (especially 1 month after initiation of RBV therapy) and RBV and ESA dosage should be adjusted when required. Practitioner may consider a prophylactic increase in ESA dosage if the patient's Hb is at the lower end of target when initiating RBV therapy.

Tac is a macrolide antibiotic which suppresses cellular immunity by inhibiting calcineurin. Its extensive red blood cell (RBC) distribution produces blood:plasma ratios ranging from 11 to 114.¹¹ Whole-blood Tac concentrations were better correlated with kidney function impairment than with plasma concentrations (obtained at 20–25°C by centrifugation). Because of difficulty in accurately measuring plasma Tac concentrations (since RBC binding is temperature dependent), whole-blood samples are used in therapeutic monitoring. In animal (rabbit) model, Tac was shown to be a low extraction/low clearance drug.^{12,13} Diffusion of Tac from RBC to plasma is slow; this slow movement and strong binding to RBC may protect part of the drug from extraction during hepatic first pass. In other words, 'the higher Hct sequesters the drug, thus protecting it from extraction by the liver, while generating lower plasma concentrations'. This phenomenon was

observed in pregnant women whose Hct was lower during pregnancy and returned to baseline postpartum.¹⁴ 'The mean Tac clearance based on whole-blood concentration was higher by 39% during mid/late pregnancy than postpartum'; correspondingly, Tac dose requirement increased during pregnancy and reduced postpartum. In our patient, Tac whole-blood concentration dropped from 6 ng/mL to an undetectable level when his Hct level reduced to half of baseline reading and level increased after his Hct returned to baseline. The clinical significance of this decrease in whole-blood Tac level secondary to anaemia is unclear. Generally, we believe only the free fraction of a drug in plasma is the active moiety; there is no direct evidence to prove whether this is true for Tac. So the decision to increase Tac dosage based on a lower Tac whole-blood concentration induced by anaemia is debatable. Nevertheless, our case reminds practitioners to take account of changes in RBC counts when interpreting Tac levels, for example, after significant blood loss postsurgery.

Learning points

- ▶ Glecaprevir/pibrentasvir (sofosbuvir-free regimen) may be the preferable option for treating hepatitis C virus genotype 3-infected individuals on haemodialysis (HD).
- ▶ Monitor haemoglobin (Hb) at least every 2 weeks after initiation of ribavirin (RBV) therapy in patients on HD and adjust RBV and erythropoietin stimulating agents (ESA) dosage accordingly; travelling to areas without monitoring facilities should be postponed.
- ▶ Consider a prophylactic increase in ESA dosage if Hb of patients on HD is at the lower end of target when RBV therapy is initiated.
- ▶ When interpreting tacrolimus levels (especially when a drastic change is not expected), take account of changes in red blood cell counts.

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