CASE REPORT

Ombitasvir/paritaprevir/ritonavir plus dasabuvir regimen may be used safely in combination with sirolimus for the treatment of chronic hepatitis C

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Accepted 21 May 2018

SUMMARY

The era of direct acting antivirals has revolutionised the management of chronic hepatitis C infection and improved patient outcomes. The optimal management of patients who require liver transplantation remains a matter of ongoing discussion. Treatment in the post-transplantation setting may be complicated by significant drug–drug interactions between antiviral agents and standard immune suppressive treatment regimens. We describe what we believe to be the first reported case of a patient successfully treated for CHC with ombitasvir/paritaprevir/ritonavir plus dasabuvir, while taking sirolimus following liver transplantation.

CASE PRESENTATION

The case we describe is of a 65-year-old man with genotype 1a chronic hepatitis C (CHC) infection. He underwent liver transplantation in the late 1990s for decompensated disease but developed graft cirrhosis with clinical decompensation and de novo hepatocellular carcinoma for which he received a second graft in 2009. His immune suppressive regimen was initially tacrolimus, azathioprine and prednisolone. At 12 months post-transplantation, he was managed successfully with sirolimus monotherapy. This was commenced in view of adverse neoplastic histological features from the explant and development of calcineurin inhibitor-related renal dysfunction. In 2011, he was treated with pegylated interferon- α and ribavirin for recurrent hepatitis C. Unfortunately, he relapsed 24 weeks after completion of a 48-week course of therapy. Staging percutaneous liver biopsy was performed in 2013 (4 years post-transplantation) which showed severe fibrosis with mild necroinflammatory changes and borderline steatohepatitis.

TREATMENT

In late 2015, he was commenced on ombitasvir/paritaprevir/ritonavir 12.5/75/50mg tablet with dasabuvir 250mg and ribavirin 200mg once daily. A reduced dose of ribavirin was used in view of stage 4 chronic kidney disease with a baseline creatinine of 250 μ mol/L. In the first 12 weeks of treatment, he suffered with troublesome symptoms of irritability and sleep disturbance which dissipated with ongoing treatment and he completed the intended course duration of 24 weeks.

His medications prior to starting antiviral treatment were: alfacalcidol 250ng three times per week, allopurinol 100mg once daily, amlodipine 10mg once daily, bisoprolol 5mg once daily, Adcal D3 one tablet twice daily, pravastatin 20mg once daily, ramipril 5mg once daily and sirolimus 1mg on alternate days. Amlodipine and pravastatin were reduced in view of potential drug–drug interactions.

Sirolimus was continued at a reduced dose throughout the therapy. Prior to commencing antiviral treatment, he was taking 1mg sirolimus on alternate days with trough levels between 2.5 and 4 μ g/L. He took a 1mg tablet of sirolimus on day 1 of treatment and levels were measured on days 4, 7, 10 and 14 of treatment to determine an appropriate interval before a subsequent dose. On day 4, the trough sirolimus level peaked at 9.3 μ g/L. On days 7 and 10, the levels had fallen to 7.1 μ g/L and 5.3 μ g/L, respectively. The next dose of 1mg of sirolimus was given 14 days after commencing antiviral treatment. Further trough levels were taken weekly for the following 2 weeks. He continued on 1mg sirolimus per fortnight for the remainder of the antiviral treatment course with levels predominantly in the range of 4–9 μ g/L (figure 1).

OUTCOME AND FOLLOW-UP

Biochemically, he remained stable throughout therapy with no significant alterations in renal function, liver biochemistry or haematological parameters. His alanine aminotransferase (ALT) remained at the pretreatment level of 50–70 U/L until the end of treatment. Since that time, the ALT along with the rest of his liver biochemistry has been normal. His HCV (hepatitis C virus) RNA was undetectable at week 2 of treatment and then consistently throughout treatment. He achieved sustained virologic response (SVR) at 12- and 24- weeks post treatment and has had no clinical complications during 9 months of follow up post treatment.

We believe this be the first reported case of a patient successfully treated for CHC with ombitasvir/paritaprevir/ritonavir plus dasabuvir, while taking sirolimus following liver transplantation.

DISCUSSION

End-stage liver disease due to CHC remains a leading indication for liver transplantation. Recurrent infection of the transplanted liver is universal

To cite: Dolman GE, Selby P, Gelson WT. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224664

Figure 1 Sirolimus levels during antiviral therapy.

and often manifests with an accelerated, progressive fibrosis. Historically, as many as a third of patients develop liver cirrhosis within 5 years of transplantation.

The availability of oral direct acting antiviral agents (DAA) has led to a paradigm shift for patients with CHC post-transplant, but there are ongoing challenges because of the significant drug–drug interactions. The most challenging of these in the most transplant setting is the effect that some DAAs have on immune suppressive regimens.

Sofosbuvir is an NS5B polymerase inhibitor which has been shown to be effective against all genotypes of hepatitis C. A multicentre study of sofosbuvir in combination with ribavirin was performed in a population of transplant recipients predominantly infected with genotype 1. The SVR12 rate of 70% would no longer be acceptable in the pretransplant setting, but the improved tolerability over conventional therapy made this an exciting step forward for those with recurrence post-transplantation.¹

The SVR12 rate improves significantly when sofosbuvir is used in combination with the second generation NS3/4 protease inhibitor, Simeprevir. A large study of 123 patients with genotype 1 recurrence post-transplant and histological evidence of disease demonstrated an SVR12 rate of 90% with an acceptable side effect profile, despite two serious events. Ribavirin was used in 20% of cases but did not appear to alter SVR rates. The interactions with ciclosporin and tacrolimus were not clinically challenging and no patients required treatment for rejection during the study.²

The combination of daclatasvir, an NS5A inhibitor with sofosbuvir has been shown to achieve SVR12 of 95% in patients with genotype 1 infection post-transplant and 82% SVR12 in those with cirrhosis (ALLY-1).³ These findings have been replicated the real-world setting with SVR12 rates of 94% in a European cohort of patients at high risk of death or decompensation within 12 months as a consequence of HCV-related graft cirrhosis.⁴ Drug–drug interactions were not significant. Sofosbuvir has also been combined with ledipasvir, an NS5A inhibitor and concurrent ribavirin. A large clinical trial included 111 patients with HCV recurrence post-transplantation, of whom the majority were infected with genotype 1. There did not appear to be significant interactions with immune suppressive regimens. The SVR12 rate was 96% in those with Child-Pugh A disease and 85% in those with Child-Pugh B disease. In those with Child-Pugh C disease (n=9), the SVR12 rates were

improved from 60% to 75% in the group that received 24 weeks rather than 12 weeks of treatment.⁵

In England and Wales, access to treatment for CHC is offered on strict guidelines from the funding body (NHS England) and at present there are no specific caveats or exceptions to these protocols for patients who have CHC post-transplant. In this case, ombitasvir/paritaprevir/ritonavir/dasabuvir was offered on a compassionate basis by Abbvie Pharmaceuticals.

Ombitasvir, an NS5A inhibitor, is co-formulated with the ritonavir-boosted protease inhibitor paritaprevir, the non-nucleoside NS5B polymerase inhibitor dasabuvir and ribavirin. A prospective study of this regimen over 24 weeks enrolled 34 patients with post-transplant HCV, none of whom had more than mild fibrosis. The treatment regimen was well tolerated with common side effects of fatigue, headache and cough. Five patients required erythropoietin and none required a blood transfusion. Eighty-five per cent of these patients were on tacrolimus, the remainder on ciclosporin. Tacrolimus was typically reduced to a dose of 0.5 mg every 10 days or 0.2 mg every 5 days. There were no episodes of graft rejection. The combination proved exceptionally efficacious with 33/34 (97%) patients achieving SVR24. A recent study from real clinical practice included 21 liver transplant recipients treated with the 3D+R regimen of whom 100% achieved SVR12. In this retrospective review, one patient developed renal insufficiency as a consequence of tacrolimus despite dose reduction but there were no episodes of graft rejection.⁶

The 3D+R regimen is associated with significant interaction with calcineurin inhibitors due predominantly to interference with CYP3A-mediated metabolism. The half-life of ciclosporin is predicted to increase from 7 to 25 hours and in the case of tacrolimus from 32 to 232 hours.⁷ As such, the clinical approach is to reduce dosing of tacrolimus and monitor carefully throughout antiviral treatment.

Sirolimus, an mTOR inhibitor, is a substrate of CYP3A4 and there is a predicted interaction between the combined treatment regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir due to inhibition of CYP3A4 by ritonavir.^{8,9} To our knowledge, this is the first clinical case reported in which sirolimus has been co-administered with the 3D+R regimen of DAA. We were unable to find any pharmacokinetic studies to guide dosing; however, limited data were available for dose adjustments of sirolimus when used with ritonavir-boosted HIV protease inhibitor regimens following kidney and pancreas transplantation, including national recommendations¹⁰ and a single case study.¹¹ We managed the potential interaction with a pre-emptive dose reduction of sirolimus and intensive monitoring until a steady state was achieved. Of note, it was only possible to safely embark on this strategy with in-house testing for trough sirolimus levels. Measured concentrations of sirolimus vary depending on whether a chromatographic method or an immunoassay is utilised. It is important to use the same assay throughout monitoring to avoid misinterpretation of results.¹² Using this strategy, our patient successfully completed the course of DAA and achieved SVR24 without any serious adverse events.

Sirolimus levels will increase when taken in combination with ombitasvir/paritaprevir/ritonavir/ dasabuvir. We recommend:

- Patients with pre-treatment sirolimus levels at the higher end of the therapeutic range should have their usual dose halved on day 1 of antiviral treatment. Patients with lower baseline sirolimus levels could take their usual dose on day one of antiviral treatment.

- After day 1 of treatment, sirolimus should be withheld and trough levels measured on day 7. Further dosing intervals should be determined on the basis on the day 7 result, with weekly monitoring until a stable dosing regimen is established.

Patients should be treated at centres with pathology services that can provide rapid sirolimus level testing.

SUMMARY

This report of a patient with significant fibrosis from recurrent HCV post-transplantation demonstrates that it is possible to administer sirolimus concurrently with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin. Our patient achieved SVR and did not develop any serious adverse events during treatment. This strategy required a significant dose reduction in sirolimus as anticipated from the pharmacokinetics of the drugs. Close monitoring for toxicity or inadequate levels of immune suppression is mandatory if this approach is adopted.

Learning points

- Chronic hepatitis C (CHC) can lead to rapidly progressive liver fibrosis post liver transplantation.
- Treatment of CHC after liver transplantation with direct-acting antivirals is complicated by drug–drug interactions.
- It is possible to successfully treat patients on sirolimus with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin.
- Dose reduction of sirolimus and close monitoring for toxicity are mandatory to avoid adverse effects.

Acknowledgements The patient described in this case received the Abbvie 3D regimen on a compassionate access programme, sponsored by Abbvie.

Contributors PS and WTG were involved directly in the management of clinical case described. Medical notes were summarised and the figure produced by GED. All the authors drafted and approved the case. All authors agreed to be accountable for the integrity of the case presented.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests WTG has given educational presentations for Abbvie and Gilead. He has also received meeting attendance grants from Abbvie and Gilead. He has provided consultancy work for Gilead. GED and PS have no financial disclosures.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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