When the wonder-drug fails: Treatment of Hepatitis C resistant to first line Direct-Acting Antiviral therapy

Sarah Fotheringham[1], Geoffrey Haar[1], Associate Professor Amanda Nicoll[2], Dr Rohit Sawhney[2]

[1]Pharmacy Department, Eastern Health, Melbourne; [2]Department of Gastroenterology, Eastern Health, Melbourne

Introduction:

It is estimated that 1.4% of the Australian population has chronic hepatitis C infection. A report in 2012 estimated associated healthcare cost to Australia at $1.5 billion over 5 years, including government sickness or disability allowances[1]. In 2016 with the introduction to market of more effective Direct-Acting Antivirals (DAAs), Australia committed $1 billion over 5 years to eradicate hepatitis C. With reported cure rates up to 95% this is certainly possible, but what about the remaining 5% of patients?

Clinical features:

A 57-year-old, Caucasian male patient was referred to Gastroenterology in 2015 in anticipation of DAA treatment for non-cirrhotic hepatitis C virus (HCV), previously non-responsive to treatment. He reported a recent increase in fatigue; however the primary treatment driver was perceived risk of sexual transmission to partner, despite safe sex practice.

Past history included hepatitis as a child (A or B, type unknown), no history of blood transfusion or tattoos and a brief period of intravenous drug use in the 1970's. First diagnosed HCV+ (Genotype 1a) in 1990, he received pegylated-interferon and ribavirin in 2010. A planned forty-eight week treatment course was ceased early at 20 weeks due to failure to achieve partial early virological response (pEVR). Fatigue and maculopapular rash were experienced during treatment.

In May 2016, following the PBS listing of DAAs, ledipasvir 90mg/sofosbuvir 400mg daily for 12 weeks was prescribed. He reported episodes of dizziness during weeks 1-4, nausea and feelings of "high energy levels" during weeks 4-12. On completion in August 2016 LFTs were normal, HVC polymerase chain reaction (PCR) was not detected and viral load was <12 IU/mL.

At follow-up (October 2016) for observation of sustained virological response (SVR), he was found to have relapsed (viral load approx. 2500 000 IU/mL, ALT 93 IU/L). Treatment compliance was reported and no concomitant medicines were received.

Interventions, Case progress and outcomes:

Testing indicated virus in this patient had a L31M variant. L31M is one of many resistance associated variants leading to slight structural differences to the NS5A protein and resistance to NS5A inhibitors (i.e. ledipasvir, daclatasvir, ombitasvir) even without prior exposure.

Literature showed no reports of successful treatment of DAA-resistant HCV1a with L31M variant. One small study[2] of treatment of DAA-resistant HCV (n=22) included one patient (genotype-1b) with L31M resistance variant who demonstrated SVR following 12 weeks' treatment with sofosbuvir, dasabuvir, paritaprevir and ombitasvir .

The following combination of DAAs was commenced for 12 weeks:

- Sofosbuvir 400mg daily
- Dasabuvir 250mg twice a day
- Paritaprevir 75mg/ritonavir 50mg/ombitasvir 12.5mg two tablets once a day
- Ribavirin 600mg twice daily

During treatment the patient reported nausea, gastrointestinal adverse effects (managed through dietary modification), fatigue and irritability (managed through lifestyle activities including yoga). On treatment completion, LFTs were normal, HVC PCR not detected with viral load <12 IU/mL.

Conclusion:

The combination of four DAAs demonstrated early virological response in a patient with treatment resistant hepatitis C. This method of treatment resulted in a sustained response and virological cure with little to no side effects.

Figure 1. Direct Acting Antiviral Targets

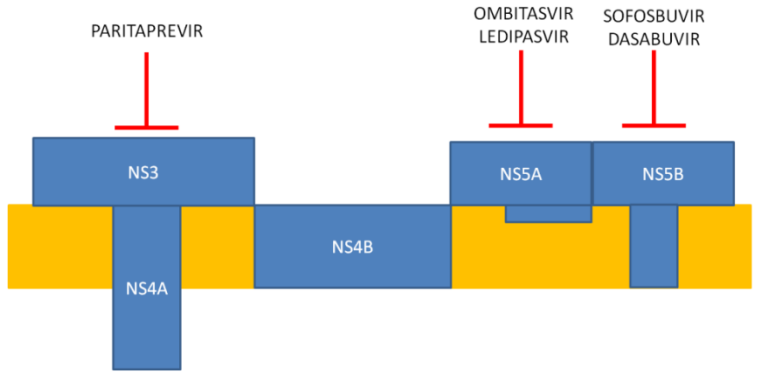
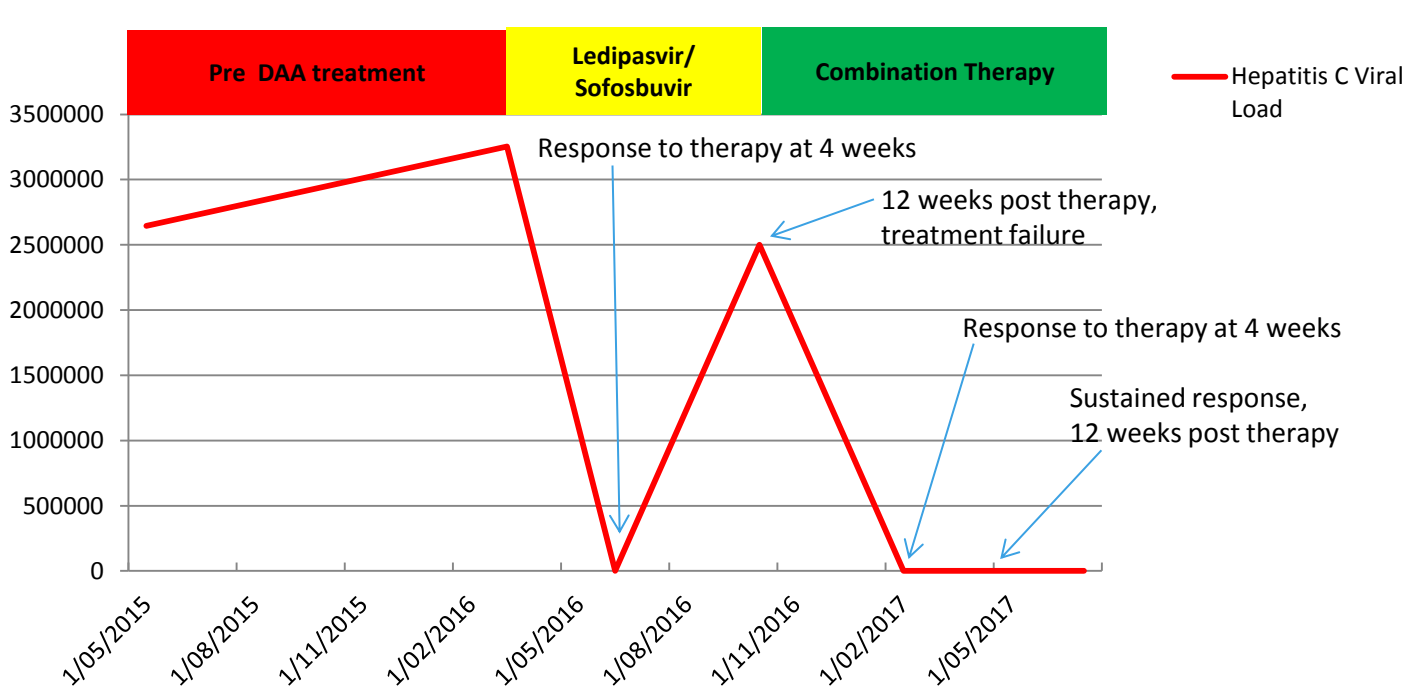


Figure 2. Comparison of Treatment Regimens

Mode of Action	First Treatment	Second Treatment
NS5A Inhibitor	✓	✓
NS5B Inhibitor (via NPI)	✓	✓
NS5B Inhibitor (via NNPI)	✗	✓
NS3/4A Inhibitor	✗	✓
Nucleoside analogue antiviral (Ribavirin)	✗	✓

Figure 3. Viral load Response to Therapy



References:

1. The Boston Consulting Group (2012) – The Economic Impact of Hepatitis C in Australia Available from http://www.hepatitisaustralia.com/s/Economic-Impact-of-Chronic-HBV-in-Aust-ACERH_RR7.pdf
2. Poordad, F, (2015). QUARTZ-I: Retreatment of HCV Genotype 1 DAA-failures With Ombitasvir/Paritaprevir/r, Dasabuvir, and Sofosbuvir. *66th Annual Meeting of the American Association for the Study of Liver Diseases*. San Francisco, California, November 13–17, 2015. Chicago, Illinois: The Henderson Company. LB20.

Contact details
Sarah Fotheringham
sarah.fotheringham@easternhealth.org.au
Geoffrey Haar
geoffrey.haar@easternhealth.org.au