Case report: successful retreatment of hepatitis C genotype 1b infection with sofosbuvir + simeprevir in a patient with cirrhosis who had prior virologic relapse after treatment with daclatasvir and asunaprevir

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Key Clinical Message
There is currently minimal clinical experience regarding retreatment options for patients failing direct-acting antiviral combination regimens. Here, we report the outcomes of a HCV genotype 1b-infected patient with virologic failure following treatment with daclatasvir and asunaprevir, who was successfully retreated with sofosbuvir plus simeprevir.

Keywords
Asunaprevir, daclatasvir, HCV, retreatment.

Introduction
The treatment of hepatitis C virus (HCV) infection has evolved from peginterferon alfa (pegIFN) plus ribavirin (RBV)-based regimens to combinations of all-oral, direct-acting antivirals (DAA), including daclatasvir – a pan-genotypic NS5A inhibitor (HCV genotypes 1–6 in vitro) – and the NS3 protease inhibitor, asunaprevir (active against HCV genotypes 1, 4, 5, and 6 in vitro). The efficacy and safety of daclatasvir and asunaprevir in combination has been assessed in multiple phase 3 studies, including the multi-cohort HALLMARK-DUAL study in treatment-naive and pegIFN/RBV-ineligible/intolerant HCV genotype 1b-infected patients from 18 countries, including Israel [1].

The sustained virologic response rate at post-treatment Week 12 (SVR12) in the overall population of HALLMARK-DUAL following treatment with daclatasvir 60 mg once daily in combination with asunaprevir 100 mg twice daily administered orally for 24 weeks was 84% (542/643) and a comparable rate in patients from Israel was observed (overall, 82% [9/11]; prior null responders, 3/3; pegIFN/RBV ineligible/intolerant, 6/8). SVR12 rates were enhanced in patients without NS5A resistance-associated variants (RAVs; L31 and/or Y93) in both the overall population (92%) and patients from Israel (7/8), and agree with similar findings from a pooled analysis of five studies in HCV genotype 1b infection [2].

Case Report
Among the patients from HALLMARK-DUAL (AI447-028; ClinicalTrials.gov number NCT01581203) who did not achieve SVR12 was a cirrhotic 58-year-old Caucasian female from Israel who had a null response to prior
pegIFN/RBV therapy and was ineligible for retreatment with pegIFN/RBV for reasons of anemia and neutropenia. The patient had HCV RNA at baseline of Log_{10} 5.43 IU/mL, no baseline NS5A or NS3 RAVs shown to result in resistance to daclatasvir or asunaprevir, and 100% compliance with respect to daclatasvir and asunaprevir dosing and treatment duration.

Pretreatment clinical laboratory abnormalities were graded according to Division of AIDs criteria V1.0. Prior to initiating therapy with daclatasvir and asunaprevir, Grade 3 elevations in total bilirubin were observed from pretreatment through on-treatment Week 2, with subsequent fluctuations between Grades 1–2 from Week 4 to resolution at follow-up Week 4. Elevations in direct bilirubin were also observed from pretreatment (9.6 × upper limit of normal [ULN]) that decreased or remained consistent at all on-treatment assessments (Week 2, 7.0 × ULN; end of treatment, 3.3 × ULN) and at follow-up Week 4 (3.0 × ULN). A pretreatment Grade 2 aspartate aminotransferase elevation resolved by Week 2, and a subsequent Grade 1 elevation during Week 4 resolved by Week 6. A pretreatment Grade 1 alanine aminotransferase elevation resolved prior to the initiation of therapy. Alkaline phosphatase levels were elevated (Grade 1) from pretreatment until follow-up Week 4.

During treatment with daclatasvir and asunaprevir, the patient experienced rapid viral decline and achieved detectable levels of HCV RNA below the lower limit of quantification (25 IU/mL) at Week 4. The patient then had undetectable HCV RNA at Week 6 that remained undetectable until relapse occurred at post-treatment Week 12 (HCV RNA was assessed at on-treatment Weeks 1, 2, 4, 6, 8, 10, and 12; and post-treatment Weeks 4, 12, and 24); HCV RNA at post-treatment Week 12 was Log_{10} 6.2 IU/mL (Fig. 1).

Population-based sequencing of the patient-derived HCV NS5A region from plasma samples collected at follow-up Week 12 revealed the emergence of signature RAVs in NS5A (L31M, Y93H [with baseline polymorphisms R30Q and P58S]) and NS3 (D168V); these substitutions confer 44,000- and 357-fold resistance to daclatasvir and asunaprevir in vitro, respectively. At follow-up Week 24 (last available sample for testing), these RAVs were still present.

On July 15, 2014, approximately 6 months after initial treatment relapse, the patient was retreated with sofosbuvir 400 mg once daily administered in combination with simeprevir 150 mg once daily administered orally for 12 weeks. An assessment of RAVs prior to retreatment was not conducted because plasma samples were not available. Sofosbuvir and simeprevir is a combination therapy that is equipotent in wild-type HCV replicons representative of HCV genotype 1b and variants with signature NS5A (L31M, Y93H) and NS3 (D168V) RAVs [3]. Retreatment baseline HCV RNA was Log_{10} 5.39 IU/mL.

Retreatment with sofosbuvir in combination with simeprevir resulted in a rapid viral decline (detectable HCV RNA below the lower limit of quantification at Week 2) that resulted in undetectable HCV RNA at retreatment Week 4. The patient achieved a SVR at both post-retreatment Weeks 12 and 24.

Figure 1. Viral decline during initial treatment (daclatasvir plus asunaprevir) and retreatment (sofosbuvir plus simeprevir). aInitial treatment with daclatasvir and asunaprevir for 24 weeks; bRetreatment with sofosbuvir and simeprevir for 12 weeks. BL, baseline; EOT, end of treatment; FU, follow-up week; HCV, hepatitis C virus.
Retreatment in this patient was generally well tolerated. The patient experienced an adverse event of mild rash between retreatment Weeks 4 and 6 that resolved without sequelae. Grade 3 elevations in total bilirubin were observed during retreatment Weeks 4, 10, and 12; a Grade 2 elevation was observed during post-retreatment Week 6. Elevations above the ULN of direct bilirubin were observed during treatment Weeks 4 (3.9 × ULN), 10 (4.4 × ULN), 12 (3.6 × ULN), and post-retreatment Week 6 (2.7 × ULN). Alanine and aspartate aminotransferase levels remained within normal limits through the treatment and follow-up periods. Elevations in thyroid-stimulating hormone were also observed during treatment Week 4 (1.2 × ULN), at end of retreatment (1.4 × ULN), and during post-retreatment Week 6 (1.6 × ULN).

**Discussion**

Overall, treatment with daclatasvir plus asunaprevir in the HALLMARK-DUAL study achieved high rates of SVR12 in HCV genotype 1b-infected patients without NS5A RAVs and with or without NS3 RAVs at baseline. This case demonstrates that in the infrequent cases of virologic failure, successful retreatment can be achieved with other all-oral, DAA regimens, even when the retreatment regimen contains the same class of drug.

Important considerations of this case report are the retreatment of a protease inhibitor–experienced patient with a second protease inhibitor–containing regimen, the absence of RAV testing prior to retreatment, and the timing of retreatment with respect to the persistence of RAVs that emerged during initial treatment.

Current European recommendations for the retreatment of patients who have failed a regimen containing one or more second-wave DAAs are based on indirect evidence (HCV genotype, resistance profiles, the number of drugs administered, use of RBV, and treatment duration) and state “Intuitively, patients who failed on a DAA-containing regimen should be retreated with an IFN-free combination including a drug with a high barrier to resistance (currently, sofosbuvir), plus one or two other drugs, ideally with no cross-resistance with the drugs already administered. Based on results in difficult-to-cure patient populations, retreatment should be for 12 weeks with ribavirin, or extended to 24 weeks with or without ribavirin (no data available comparing these approaches)” [4].

Treatment guidelines from the American Association for the Study of Liver Disease suggest that NS5A and NS3 RAV screening should be conducted prior to retreatment. It is recommended that patients without NS5A RAVs should receive retreatment with ledipasvir/sofosbuvir with RBV for 24 weeks, those with NS5A RAVs but without NS3 RAVs receive simeprevir/sofosbuvir with RBV for 24 weeks, while sofosbuvir combined with either elbasvir/grazoprevir or paritaprevir/ritonavir/ombitasvir/dasabuvir may be efficacious in patients with NS5A and NS3 RAVs (data are limited) [5].

These recommendations are based, in part, on the observations that NS5A RAVs are known to persist in the viral population for >1 year, whereas NS3 RAVs are less stable and have been shown to be gradually replaced with pretreatment NS3 sequence over time [6].

Although guidelines from both the EU and USA generally do not recommend retreatting protease inhibitor–experienced patients with a second protease inhibitor–containing regimen, successful retreatment with such regimens has been reported. Examples include daclatasvir/asunaprevir for the retreatment of IFN/RBV/telaprevir-experienced patients (SVR, 95.5%) [7], grazoprevir/elbasvir/RBV for the retreatment of IFN/RBV plus either telaprevir, boceprevir, or simeprevir–experienced patients (SVR, 96.2% [91.2% in patients with baseline NS3 RAVs and 66.7% in patients with both NS3 and NS5A RAVs at baseline]) [8], and sofosbuvir/simeprevir with or without RBV for the retreatment of patients with experience of either telaprevir, boceprevir, paritaprevir, or GS-9451 (SVR 93%) [9].

In the study of sofosbuvir/simeprevir with (n = 10) or without (n = 5) RBV for the treatment of protease inhibitor–experienced patients, an overall SVR rate of 93% (n = 14/15) was achieved after a 12-week treatment duration in a patient population that was considered to have “difficult to cure” characteristics for this regimen (HCV genotype 1a, high baseline viral levels, and prior non-response to protease inhibitors). The single patient who did not achieve SVR12 received sofosbuvir/simeprevir plus RBV and did not have NS3 RAVs associated with resistance 9 months prior to treatment. Of note, no patients had evidence of significant NS3 RAVs (three patients had NS3-Q80K, all of whom, including one recipient of sofosbuvir/simeprevir without RBV, achieved SVR12) and the majority of patients received prior protease inhibitor–based therapy >1 year prior to retreatment [9]. This study and the current case report demonstrate that high rates of retreatment SVR can be achieved without the use of RBV or extending retreatment duration to 24 weeks. The addition of RBV and extension of treatment duration to 24 weeks is recommended in treatment guidelines as mechanisms to increase response, and delay or prevent the emergence of RAVs, particularly when low barrier DAAs (e.g., protease inhibitors) are used [4, 5].

The studies described above show that retreatment of protease–experienced patients with a second protease inhibitor–containing regimen can be successful in carefully
considered cases, despite no clear guideline support for this approach. Central factors in the success of this approach are the absence of significant cross-resistance between the two regimens, and the timing of retreatment with respect to RAV fitness and survivability.

As previously noted, plasma samples prior to retreatment for RAV screening were not available, and retreatment with sofosbuvir plus simeprevir occurred 7 months after the initial treatment failure with daclatasvir plus asunaprevir. This delay in retreatment may have allowed NS3 RAVs to be replaced with pretreatment NS3 sequence over time [6]; thus enabling a successful virologic outcome with a regimen containing the same HCV inhibitor class as asunaprevir (such as simeprevir). In HCV genotype 1b replicon in vitro assays, the presence of the NS3 D168V RAV, which was detected at treatment failure, results in a 280-fold loss of simeprevir activity (EC$_{50}$, 17,917 nM) [11], compared with wild-type HCV genotype 1b replicons; when tested in parallel using the same assay, the EC$_{50}$ of asunaprevir and simeprevir in the HCV genotype 1b NS3-D168V replicon were 200 nM and 5900 nM, respectively (unpublished data). The successful retreatment of this case study suggests that if NS3 RAVs were present at the initiation of retreatment, the efficacy of sofosbuvir was sufficient to compensate for reduced simeprevir activity.

In summary, this case study demonstrates that HCV genotype 1b-infected patients experiencing virologic failure with daclatasvir plus asunaprevir therapy have potential retreatment options, including regimens containing a component with a shared mechanism of action as the initial treatment.

Consent
Written informed consent was obtained from the patient for publication of this case report.

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Conflict of Interest
R. Safadi is an academic member at the Hadassah Medical Organization and served as an advisory consultant of Bristol-Myers Squibb. N Boparai and F McPhee are employees of Bristol-Myers Squibb. S Noviello is an employee and stock holder of Bristol-Myers Squibb.

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