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MAJOR ARTICLE

Re-treatment of Hepatitis C Infection After Multiple Failures of Direct-Acting Antiviral Therapy

Daniel S. Fierer[1] and David L. Wyles[2]

[1]Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, New York, USA, and [2]Division of Infectious Diseases, University of Colorado School of Medicine, Aurora, Colorado, USA

Background. Direct-acting antiviral (DAA) therapies for hepatitis C virus (HCV) result in initial cure rates of 95% to 99% and re-treatment cure rates of 95%. Nevertheless, given the sheer magnitude of infected persons, some will ultimately fail multiple DAA therapies, and re-treatment of these persons has not been adequately studied.

Methods. We evaluated treated an HIV-infected man with cirrhosis from genotype 1b HCV who had failed 3 DAA regimens.

Results. We treated and cured our "particularly difficult-to-cure" patient with sofosbuvir plus glecaprevir/pibrentasvir plus ribavirin for 24 weeks. We discuss the literature on potential biological factors behind his treatment failures such as lack of HCV seroconversion during his infection course, and multiple failures of hepatitis B seroconversion after vaccination, and the rationale for choosing his curative salvage regimen.

Discussion. There are no clinical trials-proven re-treatment regimens for "particularly difficult-to-cure" patients. Multiple patient- and virus-related factors that do not affect cure rates in treatment-naive patients may need to be considered in choosing a re-treatment regimen for these patients. These regimens may need to include combinations drugs that are not available in single-tablet form, addition of ribavirin, and longer durations of treatment than standard.

Keywords. cirrhosis; complex DAA failure; HIV infection; particularly difficult to cure.

At the time of the advent of modern all-oral direct-acting antiviral (DAA) therapies in the United States in 2015, there were least 3.5 million persons actively infected by hepatitis C virus (HCV) [1]. These modern DAA therapies have dramatically improved cure rates compared with interferon-based treatment of chronic HCV, including among "particularly difficult-to-cure" patients, such as those with HIV co-infection, cirrhosis, unfavorable interferon lambda 3 (IFNL3, formerly IL28B) polymorphisms, and other factors [2–4]. Despite the high cure rates of 95% to 99%, even among particularly difficult-to-cure patients, the sheer magnitude of persons infected with HCV means that a substantial number will fail their first DAA therapy, which can result in drug resistance, potentially limiting re-treatment options. Studies of re-treatment after an initial DAA failure have shown that effective strategies include either the addition of active agents (other DAA classes and/or ribavirin [RBV]), using longer treatment courses, or both. With these strategies, re-treatment of those who failed firstline DAA therapies has resulted in cure rates of >95% [5], but, again, the sheer number of persons treated twice means that a substantial number will eventually fail 2 DAA regimens. For this group, there is almost no information about what regimens or durations represent viable therapeutic options. Further, the stakes are high for these multiply DAA-treated persons, as no new drugs are currently in advanced stages of development to address this issue, so were they to fail another regimen, the patients would be unlikely to have clinically validated treatment options. We present the case of a patient who illustrates this dilemma of multiple DAA failures whom we elected to treat with a combination of the available DAA classes as well as RBV, and for a longer duration than has been previously evaluated, to try to avoid his failing this treatment course, after which there would be no alternatives available for the foreseeable future.

METHODS

Case Patient

A 55-year-old man with HIV infection and a history of AIDS and chronic genotype (gt) 1b hepatitis C virus infection was referred in 2016 after failing 2 interferon-free direct-acting antiviral regimens. He was diagnosed with HIV infection in 1992 and subsequently with AIDS (pneumocystis pneumonia and CD4 count of 2 cells/μL) in 1999. He was diagnosed with HCV infection in 2005, acquired either through sex with men or sharing of injection equipment. Treatment with pegylated

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Correspondence: Daniel Seth Fierer, MD, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1009, New York, NY 10029 (daniel.fierer@mssm.edu).

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interferon (IFN) plus ribavirin (RBV) was attempted in 2007, but was stopped after 2 months due to side effects; he was not willing to be treated again using IFN. By 2013, he had evidence of progression to compensated cirrhosis, with an AST-to-platelet ratio index (APRI) of 3.7 and fibrosis-4 (FIB-4) of 5.8; his HCV antibody (Ab) test remained negative despite at least an 8-year duration of infection and HCV viral load (VL) of 7 million. In early 2015, his CD4 count was 532 cells/μL, 17%, and his HIV VL was 853 copies/mL. He was treated with a 12-week course of ledipasvir/sofosbuvir (LDV/SOF), missed no doses during treatment, and had a not-detected VL 2 weeks after completing treatment, but he had a VL of 4 500 000 IU/mL with gt 1b HCV 18 weeks after completing treatment (Table 1). He had no identified risks for re-infection, including by his partner, who also had HIV and HCV infections and who had been treated at the same time and cured of his HCV infection. In early 2016, with the availability of elbasvir/grazoprevir (ELB/GRZ), he was re-treated with the addition of RBV 600 mg twice daily for 12 weeks. His week 2 on-treatment VL was not detected (assay lower limit of quantification, 15 IU/mL). He completed treatment without missing doses, but at his first post-treatment measurement, 17 weeks after completing treatment, his VL was 932 000 IU/mL. The HCV genotype remained 1b (Table 1). He had no identified risks for re-infection. He was then referred to one of us (D.S.F.) for further treatment.

Physical examination was significant for absence of spider angiomata, a firm liver edge palpable 4 cm below the right costal margin, and lack of palpable spleen. Laboratory studies were significant for hemoglobin 15.4 g/dL, platelet count 92 000 cells/μL, international normalized ratio 0.9, albumin 3.9 mg/dL, alanine aminotransferase (ALT) 128 U/L, aspartate aminotransferase (AST) 118 U/L, and total bilirubin 1.1 mg/dL. Fibrosis assessment by APRI was 2.8, FIB-4 was 4.6, and Child-Pugh class was A. Ultrasound of the abdomen showed enlarged liver without focal mass and mildly enlarged spleen. Esophagogastroduodenoscopy showed trace esophageal varices. His HCV antibody test was again nonreactive. His HCV VL was 755 371 IU/mL. HCV gt was 1b (Mount Sinai Diagnostic Laboratory). HCV RAS testing (Quest Diagnostics) showed L31M, Q54H, and Y93H/Y RAS in NS5A and S122T RAS in NS3. HCV NS5B RAS testing was not performed.

We treated him with 24 weeks sofosbuvir/velpatasvir (SOF/VEL) plus RBV 1200 mg daily starting in early 2017. His baseline HCV VL was 1 135 255 IU/mL, and his week 5 on-treatment VL was not detected, but despite not missing any doses, his week 4 post-treatment VL was 239 000 IU/mL, with gt 1b HCV. He had no identified risks for re-infection. Repeat HCV RAS testing (Monogram Biosciences) showed L31M + Y93H RAS in NS5A and no RAS in NS3 (Table 1).

On re-evaluation for re-treatment, his clinical cirrhosis status remained Child-Pugh class A. There were no data available from clinical trials to guide choice of regimen for a patient with

Table 1. Case Patient Hepatitis C Virus Treatment Regimen and Laboratory Characteristics

Year DAA Regimen Started	CD4 Count, Cells/μL, %	HIV VL, Copies/mL	IFNL3 Polymorphism	HCV Ab	APRI/FIB-4/ Child-Pugh Score	Pretreatment RAS	Pretreatment HCV VL (Genotype), IU/mL	DAA Regimen	On-treatment HCV VL	Duration, wk	Outcome
2015	532, 17	853		NEG	3.7/5.8/A	Unknown	7 017 000 (1b)	LDV/SOF	Not done (<15 not detected week 2 post-Rx)	12	Relapse
2016	n.d.	n.d.		n.d.	n.d.	Unknown	3 900 000 (not done)	ELV/GRZ + RBV	Week 2: <15 not detected	12	Relapse
2017	n.d.	<20 detected	CT	NEG	2.8/4.6/A	NS5A: L31M, Q54H, Y93H/Y; NS3: S122T	1 135 255 (1b)	SOF/VEL + RBV	Week 5: <15 not detected	24	Relapse
2018	391, 16	<20 not detected		NEG	1.4/3.2/A	NS5A: L31M, Y93H/Y; NS3: none; NS5B: not done	1 761 347 (1b)	SOF + GLE/ PIB + RBV	Week 4: <15 detected	24	SVR 12

Abbreviations: APRI, AST-to-platelet ratio index; CD4, cluster of differentiation 4; DAA, direct-acting antiviral; ELV, elvitegravir; FIB-4, fibrosis-4; GLE, glecaprevir; HCV, hepatitis C virus; IFNL3, interferon lambda 3; LDV, ledipasvir; n.d., not done; NS3, nonstructural protein 3; NS5A, nonstructural protein 5A; NS5B, nonstructural protein 5B; glecaprevir; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VL, viral load.

this extensive prior DAA treatment history, RAS profile, and clinical status including cirrhosis with portal hypertension. Due to his cirrhosis and evidence of significant portal hypertension, including small esophageal varices, we considered re-treatment to be clinically urgent and the risks of another treatment failure to be high, and we therefore chose the regimen of SOF plus glecaprevir/pibrentasvir (GLE/PIB) plus RBV 1200 mg daily for an extended duration of 24 weeks. This treatment was started in March 2018 with a treatment baseline HCV VL of 1 761 347 IU/mL. His week 4 on-treatment VL was <15 (detected), his week 9 on-treatment VL was not detected, and he attained sustained virological response (SVR) 12 (Table 1).

Of note, despite his history of at least 1 prior attempt at vaccination against hepatitis B virus (HBV), he had no detectable (<3 mIU/mL) antibody levels before his starting the described HCV treatments. Therefore, 2 months before initiating his SOF/VEL plus RBV treatment course, he began vaccination against hepatitis B using 3 × 40-μg doses of the recombinant vaccine (Engerix-B, GlaxoSmithKline) at 0, 1, and 6 months, but he had no measurable antibody response (<3 mIU/mL). He was then re-vaccinated starting 2 months before initiating his SOF plus GLE/PIB plus RBV treatment course using 4 more 40-μg doses at 0, 1, 2, and 3 months, but again had no measurable antibody response. After completing his successful treatment course with SOF plus GLE/PIB plus RBV, he was then re-vaccinated with the more potent CpG-adjuvanted recombinant vaccine (Heplisav-B, Dynavax Technologies) using 2 × 20-μg doses at 0 and 2 months, and again had no measurable antibody response. Finally, 1 year after completing successful treatment, he was re-vaccinated with 2 more 20-μg doses of the CpG-adjuvanted recombinant vaccine and achieved a protective, albeit low, antibody level of 45 mIU/mL. His HCV VL was suppressed below 20 copies/mL at all times during this vaccination process.

RESULTS AND DISCUSSION

Modern DAA therapies have dramatically improved cure rates compared with interferon-based treatment of chronic HCV for multiple traditionally "particularly difficult-to-cure patients" including those with cirrhosis and/or HIV co-infection. However, even assuming cure rates for primary treatment of 95% to 99%, treatment of all HCV-infected individuals in the United States would result in 35 000 to 175 000 treatment failures with the initial regimen, and assuming cure rates for re-treatment regimens of 90% to 95%, re-treatment of these individuals would result in 1750 to 17 500 treatment failures. Re-treatment with more potent regimens, with the addition of either more active agents (including RBV) or longer treatment courses, or both, has been shown to cure >95% of gt 1 HCV infections in those who failed firstline DAA therapies [5, 6]. However, there are few studies of re-treatment of patients who have failed more than even 1 modern DAA regimen. The paucity of studies is somewhat due to the limited number of additional agents available, but additionally, there has been a relatively short time since the availability of modern DAA and therefore insufficient time for sequential clinical trials to have been performed. Importantly, as the actual availability of modern DAA has been restricted by payers, both private and public, and the number of people who remain undiagnosed is far higher than anticipated, only a minority of HCV-infected patients in the United States have been treated even with a single regimen [7].

Our case was therefore unusual in his having received and failed multiple DAA regimens. He failed his initial treatment with 12 weeks of LDV/SOF, which has been shown to cure 96% (315/327) of HIV-infected patients with gt 1, and despite having the 1b subtype, which is less treatment resistant than the 1a subtype [8, 9]. At the time of this initial failure in 2015, there were, as yet, no data to support a viable re-treatment regimen. Due to the clinical urgency of our patient's cirrhosis, his primary physician therefore felt pressed to use ELB/GRZ when it became available almost a year later, in early 2016, using RBV as well. Although not currently recommended for re-treatment of DAA failures, a subsequent integrated analysis of ELB/GRZ treatment of DAA-naïve patients with gt 1b HCV found that only 1% had virological failure, suggesting the possibility that his treatment failure with this regimen could have been due to the persistence of selected NS5A resistance from his failed treatment course with LDV/SOF [10]. At that point, in early 2017, the clinical situation of our patient had outpaced the available evidence for re-treatment. There were just 2 studies to guide salvage therapy after failure of regimens containing an NS5A inhibitor. The first found that simply extending treatment with LDF/SOF to 24 weeks, without RBV, was not effective in treating those who had previously failed LDV/SOF and had NS5A resistance [11]. The second found that extending treatment to 24 weeks of SOF/VEL with the addition of ribavirin was more effective, curing 36/37 (97%) of those with gt 1 HCV who were previously treated with SOF/VEL, but these patients had received either only 8 weeks of treatment or a lower dose of VEL [12]. These lower exposures to VEL likely explain the finding that just 14% among those with gt 1 in this study harbored NS5A RAS before re-treatment. Thus, these data had limited applicability to our patient, who likely had at least 2 treatment-emergent RAS at this point. Nonetheless, again due to the clinical urgency of his cirrhosis, we felt pressed to re-treat with the best combination at that time, SOF/VEL plus RBV. But again, he suffered virological failure after this both longer and RBV-containing regimen.

At that point, in early 2018, the clinical situation of our patient had again outpaced the available evidence for re-treatment, his having sustained failures of multiple DAA regimens, including those containing NS3 and NS5A classes. There were, however, 2 new regimens that had been studied as re-treatment in patients with previous DAA failure, the fixed-dose combination of SOF/VEL/voxilaprevir (VOX) and GLE/PIB. In 1 study, SOF/VEL/VOX treatment for 12 weeks cured 45 of 45 patients with

Table 2. Guideline-Suggested Approaches to Re-treatment of Complex DAA Failures

	AASLD/IDSA [17]	EASL [16][a]
Initial NS5A failure[b]	a. SOF/VEL/VOX for 12 wk[c] or b. SOF + GLE/PIB + RBV for 16 wk[d]	a. SOF/VEL/VOX for 12 wk or b. SOF + GLE/PIB + RBV for 12 wk[e]
SOF/VEL/VOX failure or otherwise particularly difficult to cure[f]	a. SOF + GLE/PIB + RBV for 16 wk or b. SOF/VEL/VOX + RBV 24 wk	a. SOF/VEL/VOX + RBV for 12–24 wk or b. SOF + GLE/PIB + RBV for 12–24 wk

Abbreviations: AASLD, American Association for the Study of Liver Diseases; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; GLE, glecaprevir; IDSA, Infectious Diseases Society of America; NS5A, nonstructural protein 5A; PIB, pibrentasvir; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

[a]Resistance testing recommended (if available) before treatment.

[b]GLE/PIB for 16 weeks is an alternative for NS5A treatment failure without NS3 PI exposure.

[c]RBV is recommended for genotype 3 with cirrhosis or GLE/PIB failures with cirrhosis.

[d]Recommended specifically in the setting of initial GLE/PIB failure.

[e]Preferred in setting of complex RAS profile or cirrhosis with other negative predictors.

[f]"Particularly difficult-to-cure" not strictly defined; may include multiple NS5A regimen failures and GLE/PIB failure in the setting of cirrhosis with other negative predictors (eg, complex RAS profiles).

gt 1b HCV who had previously failed an NS5A-containing regimen, regardless of cirrhosis status [5]. Specific to our patient, however, this study excluded those with HIV infection, and the majority had failed only 1 prior HCV treatment, but the 2 patients who harbored the L31V and Y93H combination of RAS, which confers a >100-fold increase in EC_{50} for VEL in vitro, were cured [13]. The similar L31M and Y93H combination of RAS present in our patient confers a somewhat smaller but still substantial 40- to 50-fold increase in EC_{50} for VEL in vitro [14].

The other newly available regimen, GLE/PIB, had a potential advantage for our patient in that PIB has a better in vitro resistance profile than the other available NS5A inhibitors, including VEL [15]. This difference is most pronounced in gt 1a and gt 3 isolates harboring the Y93H variant alone or in combination with other RAS. Specific to our patient, the L31M and Y93H RAS combination in gt 1b HCV that results in a large decrease in VEL activity results in no decrease in PIB activity in vitro (0.7-fold increase in EC_{50}) [11]. An interim analysis of a study of GLE/PIB in combination with SOF and RBV for 16 weeks in patients with prior failure of multiple DAA regimens including GLE/PIB and including those with cirrhosis showed a high cure rate (SVR 12 of 20 [95%] of 21) with this approach [6]. No patients with HIV co-infection were in this analysis, only 1 participant had gt 1b infection (this patient was cured), and none had failed 24 weeks of SOF/VEL plus RBV.

Therefore, although re-treatment with SOF/VEL/VOX might have been a reasonable option for our patient, taking into account his multiple failed DAA treatments, the in vitro NS5A resistance profile, and his additional negative predictors from the IFN era, such as HIV co-infection, IFNL3 CT genotype, and compensated cirrhosis, we elected to treat the patient with the most active DAA available based on in vitro evidence: SOF plus GLE/PIB plus RBV for 24 weeks, a longer duration than had been administered in clinical trials [6]. Despite the lack of clinical data to support this specific regimen, it is 1 of those recommended within the European Association for the Study of the Liver (EASL) guidance for re-treatment of "particularly difficult-to-cure patients," defined as "those with complex NS5A RAS patterns and/or those with advanced liver disease (excluding decompensated cirrhosis) who have experienced several unsuccessful courses of treatment," of which he is clearly 1 [16]. Updated American Association of the Study of Liver Disease/Infectious Diseases Society of America (AASLD/IDSA) guidance also provides for similar treatment options in such difficult cases (Table 2) [17]. Fortunately, he was cured by this regimen, and there were no safety issues encountered. To our knowledge, this is the first report of re-treatment after such extensive prior DAA failures necessitating use of this regimen and for this extended duration. It is worth pointing out that should the patient have failed this regimen and with the expected progression of liver disease in this man who already had esophageal varices to decompensated (Child B) cirrhosis, re-treatment options would have been further narrowed, as inhibitors of HCV protease (NS3) such as GLE and VOX are relatively contraindicated in persons with decompensated cirrhosis [18].

Whether NS3 and NS5A RAS testing can improve re-treatment outcomes in patients who failed multiple DAA therapies is as-yet unproven. For instance, despite the presence of complex NS5A RAS patterns that confer high-level (>100-fold) resistance to VEL in vitro that were prevalent in a retrospective analysis of the POLARIS-1 study, no effect of these RAS on the success of re-treatment with SOF/VEL/VOX was found. PIB is predicted by in vitro resistance testing to be more active than VEL in the presence of many common NS5A RAS, but, with the caveat that there are no studies directly comparing PIB and VEL, the SVR rate of re-treatment with 3-DAA SOF-containing regimens including either PIB or VEL appears to be similarly effective [6]. EASL guidelines do advocate for RAS testing after treatment failure of a DAA regimen and favor use of the PIB-containing regimen SOF and GLE/PIB in cases of "complex" RAS profiles but do not specifically define what constitutes such a profile. AASLD/IDSA guidelines do not

specifically advocate for RAS testing after treatment failure of a DAA regimen.

A final intriguing aspect of our case is whether altered immune function that further inhibited clearance of HCV infection hepatocytes beyond that due to HIV infection/AIDS [19] and cirrhosis [19, 20] may have played some role in his multiple treatment failures. Our patient had a history of clinical AIDS with a profoundly low CD4 nadir and subsequent incomplete CD4 reconstitution; he remained HCV Ab seronegative and failed multiple attempts at vaccination against hepatitis B virus (HBV), despite using multiple high-dose courses of the traditional vaccine and 1 course of the more potent CpG adjuvant vaccine, and had the IFNL3 CT genotype.

Low CD4 count (<200 cells/μL) in HIV-infected patients, although not CD4 nadir per se, has been shown to be a risk factor for failure of DAA regimens [19, 21]. HIV has been associated with a higher rate of HCV chronicity after acute infection, a delayed antibody response [22, 23], and a small proportion never seroconvert, which is also strongly associated with CD4 count <200 cells/μL [24]. Similarly, a much lower rate of seroconversion after immunization against hepatitis B has also been noted in those with HIV infection similar to our patient [25, 26], although some data suggest that the major risk is lack of control of HIV viremia rather than low CD4 count [27]. Interferon treatment itself is significantly less effective in patients with HIV infection [28, 29], but numerous studies in the modern DAA era have demonstrated comparable responses between HIV-infected and HIV-uninfected patients. In addition, the other predictors of poor response to IFN treatment relevant to our patient, such as his unfavorable IFNL3 CT genotype, have not consistently been found to be predictors of cure with initial DAA therapy [3, 9, 30]. All of these studies, however, have been in treatment-naïve patients, and none have evaluated these factors in the setting of treatment failure and particularly not in particularly difficult-to-cure patients. Our patient's experience suggests the possibility that these factors may be 1 aspect of what characterizes particularly difficult-to-cure patients, and therefore, in those with multiple failures of DAA treatment courses, these factors may need to be considered, particularly when multiple factors are present in the same individual.

In summary, we used an extended treatment regimen of 24 weeks of SOF plus GLE/PIB plus RBV to cure our patient, who had failed multiple DAA regimens and had multiple other clinical factors that may have contributed to these treatment failures. Clinical trials have not yet been performed to guide treatment of what is currently a small group of individuals with multiple treatment failures. Due to the large magnitude of patients treated for HCV worldwide, however, even with treatment success rates of 95% to 99%, it is inevitable that there will be a significant number of patients who fail multiple regimens and who are clinically in need of curative treatment. We suggest that this regimen be considered for future study in this group of patients.

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