*Clinical Infectious Diseases*

EDITORIAL COMMENTARY

# Déjà vu All Over Again: Retreatment of HCV Direct Acting Antivirals Failures—Same Satisfactory Results, Same Unanswered Questions

**Mark Sulkowski[1] and David Wyles[2]**

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA and [2]Denver Health Medical Center, Denver, Colorado, USA

**(See the Major Article by Papaluca et al on pages e3288–95.)**

**Keywords.** Direct Acting Antivirals; retreatment; resistance associated substitutions; hepatitis C.

The introduction of direct acting antivirals (DAAs) has revolutionized the treatment of chronic hepatitis C virus (HCV) infection. We are now at point where cure after therapy is almost expected (assuming compliance) and side effects are minimal. The impact has been dramatic enough to call for the global elimination of HCV by 2030 [1]. However, in a setting where DAA therapies are applied broadly across the estimated 70 million chronically infected persons globally, a large number of people will fail to achieve cure after initial therapy [2]. In addition to the sheer number of persons expected to be treated, certain virus and disease characteristics, particularly in combination, have emerged which are associated with lower responses (90%–95% SVR) to DAA treatment, most notably cirrhosis, genotype 3 infection (GT3), and viral resistance-associated substitutions (RASs) [3–6].

Even in the setting of initial DAA failure, FDA approved re-treatment is available in the form of a pangenotypic triple drug fixed dose combination consisting of inhibitors of HCV NS5B polymerase (sofosbuvir), NS3 protease (voxilaprevir), and NS5A (velpatasvir), or SVV (sofosbuvir velpatasvir voxilaprevir). This combination showed overall high efficacy for re-treatment (96% SVR) in a single registrational trial of prior NS5A containing DAA failures [7]. The major limitation of this study was an insufficient number of patients in groups that may be at higher risk for nonresponse, precluding an adequately powered assessment of risk factors for failure. Notably the majority of virologic failures in the Bouliere study had GT3 infection and compensated cirrhosis. Several subsequent cohort studies describing outcomes with SVV retreatment of patient who had not responded to an NS5A-containing DAA regimen found similar though slightly lower SVR12 (80%–95%) [8–10]. As in the registrational study, numbers of patient from key subgroups, such as those with GT3 infection and cirrhosis, were sparse, and robust assessments of predictors of nonresponse could not be evaluated. Even more limited data exist to support the use of a similar triple drug combination of sofosbuvir plus the fixed dose combination of glecaprevir (NS3 inhibitor) and pibrentasvir (NS5A inhibitor)(GP) [11].

Determining the clinical impact of RASs on DAA treatment outcomes has also been challenging. This is due to the profound modulating effect of genotype, liver fibrosis stage, treatment history, and specific DAA regimens on treatment outcomes. Let alone also considering the variable effects specific RASs in various HCV drug targets may also impart. Despite these hurdles, data from clinical studies point to several patient and virus scenarios in which RASs negatively impact treatment outcomes [4, 12, 13]; accordingly, pretreatment RAS testing is recommended in these situations [14]. For the current discussion, the most notable of these patient and virus scenarios is the presence of the NS5A Y93H RAS in patients with genotype 3 infection and cirrhosis who are treated with the 2-drug fixed dose combination of SOF/VEL. The ASTRAL-3 study of SOV/VEL for 12 weeks in GT3 infection demonstrated lower SVR in patients with cirrhosis (91%) or the presence of baseline NS5A Y93H RAS(84%) [5]. Based on this data a subsequent trial randomized this population to SOF/VEL or SOF/VEL + RBV for 12 weeks; SVR was numerically higher in those given RBV (96% vs 91% SVR) with

Received 24 August 2020; editorial decision 25 August 2020; accepted 1 September 2020; published online September 5, 2020.

Correspondence: D. Wyles, Denver Health Medical Center, Denver, CO 80204 (David.Wyles@dhha.org).

**Clinical Infectious Diseases® 2021;73(9):e3296–9**



DOI: 10.1093/cid/ciaa1329

response in patients with baseline RASs appearing to drive the difference (SVR 95% with RBV and 84% without RBV) [13].

Of course, one of the questions at hand is do pretreatment NS5A RASs, which are significantly enriched after DAA failure, still impact treatment response when SVV is used as salvage therapy? Detailed resistance analyses from the POLARIS-1 study of SVV did not identify significant differences in treatment outcomes based on the presence of NS5A RAS [15]. However, for "high risk" groups such as patients with GT3 infection and cirrhosis, the experience was limited. Overall, SVR was 97% in GT3 participants without NS5A RASs and 93% in those with RASs.

In the setting of this uncertainty, Papaluca and colleagues present results from a retrospective cohort study of NS5A-based DAA failure retreatment (n = 97) using 12 weeks of SVV in the context of an early access program in Australia [16]. The topline results are largely in line with the prior reports finding a 90% SVR12 (82/91) in a per protocol analysis excluding those with early discontinuation, loss to follow up, or death. The cohort was notable for the inclusion of a high percentage of patients with GT3 infection and cirrhosis for whom the SVR rate was 90%. At face value, this study appears to add little insight beyond those observed in prior reports; however, a closer look at the population suggests this study could be viewed as a litmus test for SVV. The majority of patients enrolled not only had cirrhosis but also evidence of portal hypertension; in fact, they included 3 patients with Child-Pugh (CP) stage B cirrhosis (enrolled as exceptions to the protocol entry criteria) and 5 patients with CP stage A who had previously experienced hepatic decompensation. Treatment of these types of patients is not for the faint of heart, even with current DAAs, and, in particular, the use of NS3 PIs in this population may be dangerous due the potential for worsening liver disease and death [17]. Indeed, in the present study, several patients had evidence of clinical decompensation during therapy. While these patients are often between a rock and hard place with few options for clinical management, expert guidelines do not recommend the routine use of DAA regimens that include HCV PIs for such patients [14].

In this context, the data presented by Papaluca and colleagues add to the emerging clinical experience with SVV re-treatment for "high risk" patient who did not respond to prior DAA therapy, highlighting key takeaway points:

- Real world evidence remains valuable. The safety, tolerability, and efficacy of DAA regimens approved on the basis of data from well-circumscribed clinical trial populations must be validated in patients representative of the more diverse populations treated in clinical practice settings.
- Despite the remarkable safety of recommended DAA regimens, a cautious approach is needed for the treatment patients with advanced cirrhosis.
- The approach to the treatment of patient who do not achieve SVR following initial DAA therapy must be optimized since this nonresponder population is enriched for patients with advanced liver disease.
- There are no proven strategies for the re-treatment of patients who fail to achieve SVR following both first-line DAA treatment and rescue re-treatment with SVV.

While the overall results reported by Papaluca are reassuring, baseline factors that predict nonresponse to SVV re-treatment could not be determined within the cohort. This stems from the heterogenous nature of the population (expected in the setting of an expanded access protocol) and the small number of patients with non-SVR, which limited the power to determine the significance of factors that contribute to clinically meaningful differences in SVR for key subgroups. For instance, in patients with the baseline Y93H RAS in NS5A SVR rate was 90% while all patients without RASs achieved SVR, but there were only 3 patients in the no RAS group [16]. The lack of power in the study is highlighted by the observation that even established predictors of nonresponse to SVV such as cirrhosis or GT3 infection were not significant predictors of non-SVR in univariate analysis, despite the inclusion of more patients with GT3 infection and cirrhosis than the POLARIS-1 trial and previously reported cohorts [7, 9].

Accordingly, key clinical questions remain. If an 89% SVR following re-treatment with SVV is not good enough, and we would argue it is not for a population with advanced cirrhosis (eg, evidence of portal HTN), what are the next steps for the treatment of this small but critical population of "hard to cure" patients?

First, larger studies are needed to explore and identify predictors of nonresponse following re-treatment, particularly among patients with GT3 infection and cirrhosis. Given the relative rarity of this patient population, investigators will need to collaborative to combine data derived from multiple smaller HCV cohort studies. Despite the heterogeneity in the types of patients, treatment regimens and data collected, analytical approaches have been established and successful for cohort of patients with HIV infection [18]. However, since RAS testing is not routinely recommended in patients who fail first-line DAA therapy before re-treatment, these data may be conspicuously absent from most HCV cohort studies that may preclude more definitive conclusions.

Second, in the absence of definitive evidence about the impact of RASs on the response to re-treatment with SVV or other regimens, clinicians need to interpret the existing, albeit limited data, to guide decisions. Given the clinical

experience with the treatment of other chronic viral infections, such as HIV-1, and the specific circumstances with HCV therapy where RASs have been determined to impact outcome, we certainly cannot rule out a significant impact of RAS in response to retreatment of DAA failures. As such, before re-treatment, baseline NS5A RAS testing should be considered in "hard to cure" patients who fail first-line DAAs, namely those with advanced cirrhosis and GT3 infection.

Finally, if NS5A RASs are present, specifically the Y93H substitution, how would this change the re-treatment recommendation for the patient? The most straightforward answer is that we do not know. However, there are several potential considerations: 1) If the benefit of SVR is uncertain due to advanced liver disease, treatment could be deferred until after liver transplantation. Multiple trials including the Papaluca study have demonstrated excellent SVR with DAA therapy post-transplant compared to significantly lower rates of SVR in decompensated cirrhosis [19–21]. Of course, the path to liver transplantation is complicated and likely not available to many patients with advanced liver disease who fail initial DAA treatments; 2) Extension of the treatment duration to 16 or 24 weeks. Historically, longer treatment duration has been associated with higher SVR rates including in patients with baseline RASs [22]; 3) Addition of ribavirin to the DAA regimen with or without an extended duration of treatment [12, 13]. While the mechanism action of this guanosine nucleoside analogue remains elusive, randomized controlled of earlier DAA regimens, including telaprevir, convincingly demonstrated the ability of this drug to prevent the emergence of resistant virus, leading to higher SVR rates [23, 24]; and 4) Re-treatment with a "mix and match" DAA regimen based on the RAS profile instead of the fixed-dose combination of SVV. In vitro, the NS5A inhibitor pibrentasivir has greater activity against certain RASs compared to velpatasvir. For example, the Y93H RAS in genotype 3 virus has less of an impact on the antiviral activity of pibrentasivir (<3x fold-change in the EC50 compared to wild-type) than on velpatasvir (>100x fold-change in the EC50 compared to wild-type) [6, 25]. Yet, it remains unclear whether this in vitro observation confers clinical benefit in the setting of triple DAA therapy. Finally, although not an option today, the addition of a fourth pangenotypic agent with a unique resistance profile or different mechanism of action would be attractive. One potential candidate is in clinical development, a non-nucleoside inhibitor of NS5b (CC-31244) [26].

While virtually no area of medicine has come farther in the last decade than HCV treatment, key questions remain for patients with disease and treatment characteristics that make them most vulnerable to repeated antiviral therapy failure and morbidity and mortality related to advanced liver disease. Data such as those presented by Papaluca et al. provide incremental answers to these remaining questions, but we have significant clinical questions remaining to address in order to optimally treat a population that will continue to grow over the next decade.

## Note

***Potential conflicts of interest.*** D. W. reports research support to the institution from Gilead Sciences, outside the submitted work. M. S. reports grants and personal fees from Gilead Sciences, grants and personal fees from AbbVie, personal fees from Arbutus Biopharma, grants and personal fees from Assembly Bio, personal fees from Biomarin, personal fees from Immunocore, personal fees from Clinical Care Options, personal fees from ViralEd, personal fees from PracticePoint Communications, personal fees from DKBmed, grants and personal fees from the National Institutes of Health (grants K24DA034621–07; R01DA016065), grants from PCORI, outside the submitted work. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. WHO. Global health sector strategy on viral hepatitis 2016–2021. World Health Organization, Available at: http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/. Accessed 24 August 2020.
2. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol **2018**; 3:383–403.
3. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med **2015**; 163:1–13.
4. Zeuzem S, Mizokami M, Pianko S, et al. NS5A resistance-associated substitutions in patients with genotype 1 hepatitis C virus: prevalence and effect on treatment outcome. J Hepatol **2017**; 66:910–8.
5. Foster GR, Afdhal N, Roberts SK, et al; ASTRAL-2 Investigators; ASTRAL-3 Investigators. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med **2015**; 373:2608–17.
6. Hezode C, Reau N, Svarovskaia ES, et al. Resistance analysis in patients with genotype 1-6 HCV infection treated with sofosbuvir/velpatasvir in the phase III studies. J Hepatol **2018**; 68:895–903.
7. Bourlière M, Gordon SC, Flamm SL, et al; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med **2017**; 376:2134–46.
8. Belperio PS, Shahoumian TA, Loomis TP, Backus LI. Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir in 573 direct-acting antiviral experienced hepatitis C patients. J Viral Hepat **2019**; 26:980–90.
9. Llaneras J, Riveiro-Barciela M, Lens S, et al. Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs. J Hepatol **2019**; 71:666–72.
10. Degasperi E, Spinetti A, Lombardi A, et al; NAVIGATORE-Lombardia and Veneto Study Groups. Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure. J Hepatol **2019**; 71:1106–15.
11. Wyles D, Weiland O, Yao B, et al. Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection. J Hepatol **2019**; 70:1019–23.
12. Sarrazin C, Dvory-Sobol H, Svarovskaia ES, et al. Prevalence of resistance-associated substitutions in HCV NS5A, NS5B, or NS3 and outcomes of treatment with ledipasvir and sofosbuvir. Gastroenterology **2016**; 151:501–12.e1.
13. Esteban R, Pineda JA, Calleja JL, et al. Efficacy of sofosbuvir and velpatasvir, with and without ribavirin, in patients with hepatitis C virus genotype 3 infection and cirrhosis. Gastroenterology **2018**; 155:1120–7.e4.
14. Recommendations for Testing, Managing, and Treating Hepatitis C. HCV Guidance. Available at: https://www.hcvguidelines.org/. Accessed 3 May 2018.
15. Sarrazin C, Cooper CL, Manns MP, et al. No impact of resistance-associated substitutions on the efficacy of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks in HCV DAA-experienced patients. J Hepatol **2018**; 69:1221–30.

16. Papaluca T, Roberts S, Strasser SI, Stuart K, Farrell GC. Efficacy and safety of sofosbuvir/velpatasvir/voxilaprevir for HCV NS5A-inhibitor experienced patients with difficult to cure characteristics. Clin Infect Dis **2020**.
17. Research C for DE and. FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease. FDA **2019**. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and. Accessed 24 August 2020.
18. Gange SJ, Kitahata MM, Saag MS, et al. Cohort profile: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Int J Epidemiol **2007**; 36:294–301.
19. Agarwal K, Castells L, Müllhaupt B, et al. Sofosbuvir/velpatasvir for 12 weeks in genotype 1-4 HCV-infected liver transplant recipients. J Hepatol **2018**; 69:603–7.
20. Reau N, Kwo PY, Rhee S, et al. Glecaprevir/pibrentasvir treatment in liver or kidney transplant patients with hepatitis C virus infection. Hepatology **2018**; 68:1298–307.
21. Curry MP, O'Leary JG, Bzowej N, et al; ASTRAL-4 Investigators. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med **2015**; 373:2618–28.
22. Gane EJ, Shiffman ML, Etzkorn K, et al; GS-US-342-1553 Investigators. Sofosbuvir-velpatasvir with ribavirin for 24 weeks in hepatitis C virus patients previously treated with a direct-acting antiviral regimen. Hepatology **2017**; 66:1083–9.
23. Hézode C, Forestier N, Dusheiko G, et al; PROVE2 Study Team. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med **2009**; 360:1839–50.
24. Hong CM, Liu CJ, Yeh SH, Chen PJ. Addition of ribavirin to daclatasvir plus asunaprevir for chronic hepatitis C 1b patients with baseline NS5A resistance-associated variants improved response. J Formos Med Assoc **2017**; 116:295–9.
25. Ng TI, Krishnan P, Pilot-Matias T, et al. In vitro antiviral activity and resistance profile of the next-generation hepatitis C virus NS5A inhibitor pibrentasvir. Antimicrob Agents Chemother **2017**; 61:e02558–16.
26. Lee S, Pascual L, Pattassery J, Sulkowski M. Phase 1 study assessing the safety, pharmacokinetics, and antiviral activity of CC-31244, a pan-genotypic, potent non-nucleoside NS5B polymerase inhibitor for the treatment of hepatitis C virus infection. J Hepatol **2017**; 66:S720.