



Managing DAA Failures in Light of New HCV Regimen Approvals



Volume 5 Issue 9

In this Issue...

For patients failing currently available interferon-free DAA therapies, efficacious and evidence-based treatment approaches have been lacking. Concerns about selected drug resistance and its negative impact on subsequent therapies, along with a lack of suitable regimens for retreatment, have been key barriers to confidently managing these patients.

In this issue, Dr. David L. Wyles from the Denver Health Medical Center and the University of Colorado reviews several recent studies examining the risk of selecting and maintaining HCV resistance associated substitutions (RASs) following common first-line HCV therapies, along with the findings on retreatment patients, despite resistance, with newly approved regimens with increased potency and improved resistance profiles. The trials reviewed are among the first large studies devoted to retreatment of HCV in the setting of resistance, and the excellent response rates highlight the role these new regimens will have in retreatment without the need for resistance testing.

Program Information

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Length of Activity

- 1.0 hour Physicians
- 1.0 hour Nurses

Launch Date

October 26, 2017

Expiration Date

October 25, 2019

LEARNING OBJECTIVES

- Describe the risk of resistance development following unsuccessful HCV therapy containing direct acting antivirals (DAAs).
- Discuss the impact DAA resistance and other negative predictors (eg, cirrhosis) have on the effectiveness of newly approved retreatment options.
- Summarize effective retreatment strategies for patients who have previously failed HCV therapy containing a direct acting antiviral.

GUEST AUTHOR OF THE MONTH

Commentary & Reviews

Guest Faculty Disclosure

Dr. Wyles has disclosed that he has served as a consultant/advisor to AbbVie, Inc. Gilead Sciences, Inc., and Merck & Co., Inc. He has also received grant/research funding from AbbVie, Inc., Gilead Sciences, Inc., and Merck & Co., Inc.

Unlabeled/Unapproved uses

Dr. Wyles has indicated that there will be references to the unlabeled use of ribavirin with the sofosbuvir/velpatasvir/voxilaprevir combination, although such use

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is recommended in the current
HCV treatment guidelines.

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KEY TAKEAWAYS

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Direct acting antiviral therapies for hepatitis C infection are highly effective with most patients (> 90%) attaining a cure. For instance, as Wyles et al reported (in one of the reviewed papers), the virologic failure rate after treatment with sofosbuvir/ledipasvir (SOF/LDV) was only 2.4%, with most failures coming from experimental durations that are not recommended. A recent real-world analysis including over 4,000 treated patients found a DAA overall failure rate of 6.3%.¹ Risks for treatment failure included male gender, age > 60, cirrhosis, and shorter treatment regimens. However, while the absolute risk of failure is low, given the large number of persons with HCV being treated a significant number of failures will accumulate.

HCV DAA treatment failure is associated with a high rate of drug resistance development, which may further complicate retreatment approaches. Several studies highlight both the high prevalence of resistance development as well as persistence of resistance substitutions once selected. Wyles et al also (in another publication reviewed in this issue) reported on HCV resistance associated substitutions following SOF/LDV. Overall, the rate of NS5A resistance was 75% and increased to 94% if treatment was given for 12 weeks. Two additional points from this study are important: 1) most virologic failures are genotype 1a and the NS5A RASs selected confer cross-resistance to most other NS5A inhibitors, particularly in genotype 1a; 2) essentially no SOF (NS5B nucleoside) resistance was selected (< 1%), confirming that this class of antivirals will have a prominent role in retreating DAA experienced populations.

Lahser et al performed a similar study (reviewed herein) focusing on the regimen of elbasvir/grazoprevir (EBR/GZR). Findings for NS5A resistance were similar: NS3 resistance was also selected frequently, being found in 75% at failure.

Where NS3 and NS5A RASs differ is in their persistence. The study by Lahser demonstrated that most NS3-resistant variants are lost within 24 weeks of virologic failure. In contrast, both the Lahser study, as well as an additional study by Wyles et al, supported the conclusion that NS5A RASs remain enriched in the viral quasispecies for a prolonged time (> 3 years).

Prior to the approval of several of the DAA regimens covered in this review, effective retreatment strategies for DAA failures had not been established. One of the first studies to evaluate retreatment of SOF/LDV failures looked at extension of therapy with the same regimen for 24 weeks (no RBV).² While retreatment was modestly effective, with a 71% SVR, the presence of NS5A resistance prior to retreatment determined outcomes. Patients without NS5A RASs achieved a 100% SVR with retreatment while those with resistance has an SVR of 60%.

Subsequent studies that evaluated treatment extension and the addition of RBV had more success. A study of sofosbuvir/velpatasvir (SOF/VEL) failures found a 97% SVR in genotype 1-infected patients retreated with SOF/VEL plus RBV for 24 weeks.³ Genotype 3 SOF/VEL treatment failures in this study did not respond as well (78% [14/18] SVR). A medical need still exists for shorter retreatment strategies that do not require RBV and are effective for all genotypes.

To improve response rates in patients with prior DAA failure and resistance, treatment regimens must contain antivirals with new mechanisms of action and/or with improved resistance profiles. The recently approved regimen of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) combines three mechanisms of antiviral action with enhanced resistance profiles. The two phase 3 studies by Bourliere et al detailed in this issue demonstrated remarkable efficacy of this regimen in the most difficult-to-treat HCV populations. A slight decrease in efficacy was noted in the presence of cirrhosis, particularly in patients with genotype 3 infection and prior NS5A exposure. Based on the data, it seems that this population may benefit from the addition of RBV to 12 weeks of SOF/VEL/VOX, although this was not studied. A second regimen, uprifosobuvir plus grazoprevir and ruzasvir, combining the same three classes of HCV inhibitors, also performed well. However, despite the lack of virologic failures in this study (Wyles et al), 24 weeks or 16 weeks plus RBV is unlikely to be competitive when a 12 week regimen exists. Shorter studies without RBV are needed for this regimen.

Finally, the approach of using only two drug classes with excellent resistance profiles was shown to be highly efficacious in many settings, but the weakness of this approach was also



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uncovered in populations previously exposed to both classes of medications. The combination of GLE/PIB (glecaprevir, an NS3/4A protease inhibitor; and pibrentasvir, an NS5A inhibitor) yielded excellent SVR rates for retreatment of NS3 or NS5 inhibitor exposed patients (Poordad et al, reviewed herein); however when retreating a patients previously exposed to both classes of HCV drugs, retreatment response fell short of what is now expected (SVR ~ 95%). The results of this study led to the current indications for this regimen, which include retreatment of patients previously exposed to either NS3 or NS5A inhibitors (but not both).

In summary, while resistance selection is frequent when DAA treatment fails and was demonstrated to impact retreatment with similar regimens, the approval of new HCV regimens appears to have effectively addressed the previously unmet medical need for effective retreatment. These data suggest that routine resistance testing is not required to effectively retreat patients; however, detailed knowledge of prior treatment regimens and an accurate assessment of the patient's fibrosis stage remain critical.

References:

1. Sulkowski MS, Reddy KR, Nelson DR, et al. [SAT-229 - Incidence of and predictors for direct acting antiviral treatment failure among 3909 hepatitis C genotype 1 infected adults: real world outcomes from HCV TARGET](#). *J. Hepatol.* 66, S719–S720 (2017).
2. Lawitz E, Flamm S, Yang JC, et al. [Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks](#) [EASL abstract O005] *J Hepatol.* 2015;62(1) suppl.
3. 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 Oct;66(4):1083-1089.

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Resistance Profile After Failure with Sofosbuvir + Ledipasvir

Wyles D, Dvory-Sobol H, Svarovskaia ES, et al. Post-treatment resistance analysis of hepatitis C virus from phase II and III clinical trials of ledipasvir/sofosbuvir. *J Hepatol.* 2017 Apr;66(4):703-710



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Current direct acting antiviral (DAA) therapies are highly efficacious; however, a small percentage of patients may fail treatment and are at risk for resistance development. The fixed- dose combination of sofosbuvir (SOF, an NS5B nucleoside) plus ledipasvir (LDV, an NS5A inhibitor) was the first DAA fixed-dose combination approved for HCV treatment in US. This study evaluated the rate of resistance development after unsuccessful SOF/LDV treatment; in particular, rates of NS5A resistance may be important, as a prior study¹ showed that NS5A resistance may impact retreatment responses.

Patients from two phase 2 and three phase studies were eligible if they received at least one dose of SOF/LDV and had virologic failure or early discontinuation and a subsequent HCV RNA sample with a viral load $\geq 1,000$ IU/ml available for sequencing. Deep sequencing was conducted and the data analyzed using 1% and 15% detection thresholds. Companion in vitro phenotypic studies were conducted in chimeric replicons harboring patient-derived NS5A and NS5B sequences.

The virologic failure rate was only 2.4% (51: 49 relapse and 2 BT [noncompliance]), highlighting the excellent efficacy with modern DAA regimens. Genotype 1a was overrepresented in the virologic failure population, making up 75% of the patients across the five studies and 82.4% (42/51) of the virologic failure population. Note that not all patients in these trials were treated with what became the standard-of-care approaches based on data from these studies once completed. Specifically, 41% (20/49 relapses) of patients in this

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analysis received less than 12 weeks of LDV/SOF in a situation that currently would not be recommended for short-course therapy.

The virologic failure rate declined with longer treatment durations, going from 32% with six weeks of therapy to 0.5% with 24 weeks. Conversely, the rate of harboring NS5A resistance increased in those who failed after longer durations. The overall NS5A resistance rate of 74% varied between 67% in those treated for eight weeks and 95% in those treated for 12 weeks (the two durations most likely to be currently used). In patients only treated for six weeks, the rate of NS5A RAS selection was only 38% (3/8). Ribavirin did not have a clear impact on the selection of NS5A RASs at a given treatment duration. The caveat is that there are small numbers in each group and very limited power to detect any difference. However, not even a consistent trend was evident (eg, fewer RASs in RBV groups across durations were not seen).

The Y93H RAS was most commonly selected in genotype 1b. More variability existed in RASs selected in GT1a, though Q30R/H, L31M, and Y93H RASs were most common. In vitro replicon studies confirmed that these RASs all confer a > 100x increase in LDV EC50 and confer cross-resistance to daclatasvir. Velpatasvir retained activity against most of these RASs, with the exception of Y93H in genotype 1a.

As expected based on prior reports,² the selection of the signature SOF NS5B RASs (S282T) was almost nonexistent. This RAS was only seen in one genotype 1a virologic failure who also had high level LDV resistance (L31M) at baseline. While the S282T RAS was present in the majority of sequencing reads (91%) in the initial post-treatment sample, at repeat sequencing just five days later the prevalence of S282T had dropped to 8%.

References:

1. Lawitz E, Flamm S, Yang JC, et al. [Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks](#) [EASL abstract O005] *J Hepatol*. 2015;62(1) suppl.
2. Svarovskaia ES, Dvory-Sobol H, Parkin N, et al. [Infrequent development of resistance in genotype 1-6 hepatitis C virus-infected subjects treated with sofosbuvir in phase 2 and 3 clinical trials](#). *Clin Infect Dis*. 2014 Dec 15;59(12):1666-74.

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Resistance Profile After Failure with Elbasvir + Grazoprevir

Lahser FC, Galloway A, Hwang P, et al. Interim analysis of a 3-year follow-up study of ns5a and ns3 resistance-associated variants (RAVs) after treatment with grazoprevir-containing regimens in patients with chronic hepatitis C virus (HCV) infection. *Hepatology*. Baltimore, Md 64, 32A (2016).

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The fixed-dose combination of elbasvir (EBR), an NS5A inhibitor, with grazoprevir (GZR), an NS3 protease inhibitor, is a commonly used HCV DAA treatment and differs from many other fixed-dosed combinations in that it does not include an NS5B nucleoside and resistance testing is recommended prior to its use in patients infected with genotype 1a. As in other DAA regimens, overall SVR rates are expected to be high with this regimen (> 95%); however, when virologic failure occurs, resistance associated substitutions (RASs) may be selected to both components of the regimen and impact future treatment options.

This study describes the genotypic resistance patterns in all patients with genotype 1 infection and virologic failure after treatment with GZR (with or without pegylated interferon and ribavirin) in phase 2/3 trials. The majority received EBR with GZR and this summary will focus on those receiving EBR/GZR ± RBV since it is used clinically. Assessment for RASs was conducted by population sequencing at baseline (pretreatment) and at virologic failure (provided the HCV RNA was ≥ 1000 IU/mL) and included a prolonged three-year follow-up for assessment of RAS persistence. The study population included 58 patients and was

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enriched for those with GT1a infection (n = 44) and treatment with EBR/GZR ± RBV for eight to 16 weeks (37/58).

After virologic failure both NS3 and NS5A RASs were present in the majority of patients treated with EBR/GZR. NS3 RASs were present in 75% (27/36) including 23/36 (64%) with treatment emergent RASs. Treatment-emergent RASs, excluding the Q80K, which is prevalent at baseline and has no in vitro impact on GZR, were enriched for A156T and D168A/G/V variants, which result in > 5x resistance to GZR in vitro. At failure NS5A RASs were detected in 94% (34/36) including 78% with treatment emergent NS5A RASs. Baseline NS5A RASs can impact EBR/GZR efficacy, so in this case the total with RASs at failure is clinically relevant. Still a shift in NS5A RAS prevalence was seen with L31M predominant at baseline and Q30R/H and Y93C/H/N seen at failure.

Prior studies have indicated that NS3 RASs tend to be outgrown by wild-type virus quickly following cessation of drug selective pressure, while NS5A RASs remain enriched for prolonged periods.^{1,2} The up to three-year sequencing follow-up in this study provides important additional data. The mean time to reversion of treatment emergent NS5A RASs was 12 weeks, with over 80% lost by population sequencing between 24 and 36 weeks of follow-up. The rapid loss appeared to be due in part to the initial selection of A156T and D168 variants, which have poor replicative fitness in vitro. No selected A156 or D168 treatment-emergent variants remained detectable at week 36 (most were lost by week 12). In contrast, nearly all treatment-emergent NS5A RASs remained detectable by population sequencing (94% [33/35]) through week 96. This included all Q30 variants and 8/9 Y93 variants, which result in resistance to EBR and most other NS5A inhibitors.

References:

1. Sullivan JC, De Meyer S, Bartels DJ, et al. [Evolution of treatment-emergent resistant variants in telaprevir phase 3 clinical trials](#). *Clin Infect Dis*. 2013 Jul;57(2):221-229.
2. Wyles D, Mangia A, Cheng W, et al. [Long-term persistence of HCV NS5A resistance associated substitutions after treatment with the HCV NS5A inhibitor, ledipasvir, without sofosbuvir](#). *Antivir Ther*. 2017 Jun 26.

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Long Term Persistence of NS5A RASs

Wyles D, Mangia A, Cheng W, et al. Long-term persistence of HCV NS5A resistance associated substitutions after treatment with the HCV NS5A inhibitor, ledipasvir, without sofosbuvir. *Antivir Ther*. 2017 Jun 26.

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Resistance associated substitutions (RASs) are frequently selected after unsuccessful HCV therapy containing NS5A inhibitors. Early reports suggested that NS5A RASs may persist for prolonged periods, particularly compared to RASs selected in NS3, with the potential to adversely impact subsequent HCV treatment regimens containing NS5A inhibitors.¹⁻³ This 2017 manuscript describes the post-treatment evolution of NS5A RASs following viral relapse after therapy containing ledipasvir (LDV). Patients enrolled in the study were treated in one of several phase 2 studies of LDV in combination with other DAAs and with or without interferon/ribavirin. Importantly, no patient received SOF with LDV and the other DAAs included in these regimens (an NS3 PI and NS5B non-nucleoside) were not further developed as HCV therapeutics. Of note, the rate of virologic failure in these studies was higher than that seen with SOF/LDV.⁴

Sequencing was performed on plasma or serum samples with an HCV RNA ≥ 1,000 IU/ml at virologic failure in the parent study (population sequencing) and at entry (deep sequencing) into the registry study as well as at weeks 12, 24, 48, and 96 of follow-up (all deep sequencing). Sequencing cutoffs of 1% and 15% were examined when deep sequencing was performed. Pretreatment population sequencing of the NS5A gene was conducted to ascertain the prevalence of NS5A RAS in the study population prior to LDV exposure.

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Pretreatment sequencing for NS5A RASs was available in 76 patients who went on to have virologic failure. Post-virologic failure sequencing was performed on at least one follow-up sample in 73 of the 76 patients. At virologic failure, nearly all patients had detectable NS5A RASs (99%, 72/73). Among the 14% with pretreatment RASs (11/76) additional posttreatment NS5A RASs were present in 8/11 and at least one NS5A RAS persisted though 96 weeks in all 11 (100%). The majority of patients with treatment-emergent NS5A RASs (n = 65) also had multiple sequencing timepoints completed including 59/65 at week 96 post-therapy; at week 96, 78% of the patients with only treatment-emergent RASs continued to have detectable NS5A RASs by deep sequencing at a 15% threshold.

While at least one NS5A RAS remained detectable in most patients, the number of RASs per patient was seen to decline over time. At entry into the registry 23% of patients had ≥ 3 RASs; however, by week 96 it was down to 12%. When assessed by genotype 1 subtype, different patterns were also observed. Genotype 1a patients tended to select for more and variable RASs (Q30R/E, L31M, H58D, and M28T) compared to 1b (L31 variants and Y93H). Rates of persistence to week 96 by genotype were similar (1a 78% at week 96; 1b 80% at week 96).

References:

1. Sullivan JC, De Meyer S, Bartels DJ, et al. [Evolution of treatment-emergent resistant variants in telaprevir phase 3 clinical trials](#). *Clin Infect Dis*. 2013 Jul;57(2):221-229.
2. Lahser FC, Galloway A, Hwang P, et al. [Interim Analysis of a 3-Year Follow-up Study of NS5A and NS3 Resistance-Associated Variants \(RAVs\) After Treatment With Grazoprevir-Containing Regimens in Patients With Chronic Hepatitis C Virus \(HCV\) Infection](#). *Hepatology*. Baltimore, Md. 64, 32A (2016).
3. Lawitz E, Flamm S, Yang JC, et al. [Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks](#) [EASL abstract O005] *J Hepatol*. 2015;62(1) suppl.
4. Wyles D, Dvory-Sobol H, Svarovskaia ES, et al. [Post-treatment resistance analysis of hepatitis C virus from phase II and III clinical trials of ledipasvir/sofosbuvir](#). *J Hepatol*. 2017 Apr;66(4):703-710.

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Triple-Drug Combination for HCV Retreatment After DAA Failure

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 Jun 1;376(22):2134-2146.



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This manuscript presents the results of two phase 3 trials of the fixed dose combination of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) in patients infected with HCV of any genotype and had previously failed HCV treatment including a direct-acting antiviral (DAA). The POLARIS-1 study evaluated 12 weeks of SOF/VEL/VOX in DAA-treated patients whose prior regimen included an NS5A inhibitor; a population representing the most difficult patients to retreat. This study included a deferred treatment arm (only for genotype 1) given placebo for the first 12 weeks followed by open-label active treatment. The POLARIS-4 study was a randomized, blinded study comparing 12 weeks of SOF/VEL/VOX to 12 weeks of SOF/VEL in patients who had previously failed a DAA regimen that did not contain an NS5A inhibitor (NS3 PI, SOF or both). Both trials allowed patients with compensated cirrhosis to enroll. Ribavirin was not evaluated in any of the treatment arms.

Aside from differences in the prevalence of baseline resistance associated substitutions (RASs) reflecting different prior DAA exposures, the populations were very similar across the POLARIS 1 and 4 studies. The population was predominately male (75-79%), genotype 1a

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(29%-38%) or 3 (30%-34%) predominant, with high rates of cirrhosis (46%). In POLARIS-1 the most common prior regimen was an NS5B nucleotide plus an NS5A inhibitor (61% of patients). In POLARIS-4 most patients (72%) were previously only exposed to a single DAA, an NS5B inhibitor, presumably with RBV with or without interferon. The prevalence of NS3 and/or NS5A RASs at baseline mirrored prior DAA exposure and was higher in POLARIS-1 (83% with NS3 or NS5A RASs).

Topline results for SVR12 were impressive in both studies. In the immediate treatment arm of POLARIS-1, 96% of patients achieved SVR (ITT; 95% CI: 93%-98%). Broken down by genotype, SVR rates were 96% for GT1a (97/101), 95% for GT3 (74/78) and 91% for GT4 (20/22); 100% SVR was seen in all other genotypes, although only GT1b (n = 45) had significant numbers. The presence of cirrhosis appeared to have an impact on response, with a 99% SVR in patients without cirrhosis and 93% SVR in those with cirrhosis. An identical 93% SVR was seen in patients with GT3 and cirrhosis (52/56). In contrast to cirrhosis, an impact of baseline RASs was not apparent with a 97% SVR in those with baseline RASs (199/205). Finally of the 10 non-SVRs, seven were virologic failures. The lone patient with HCV RNA breakthrough on study had low drug levels indicative of noncompliance. Of the remaining six with virologic failure, most were GT3 with cirrhosis (4/6).

In POLARIS-4, SOF/VEL/VOX for 12 weeks outperformed SOF/VEL for 12 weeks with SVR of 98% and 90% respectively. The largest differences between SOF/VEL/VOX and SOF/VEL were seen in patients with GT1a and GT3 (98% vs 89% and 96% vs 85%, respectively) and in those with cirrhosis (98% and 86%, respectively). The differential rates for cirrhosis were driven by GT1a and GT 3 as well. Again, no impact of baseline resistance was noted for either regimen. Virologic failure rate was higher with SOF/VEL (10%) compared to SOF/VEL/VOX (1%).

SOF/VEL/VOX was well tolerated in both trials; however higher rates of diarrhea were seen with SOF/VEL/VOX compared to placebo (18% vs 12%, respectively) or SOF/VEL (20% vs 5%, respectively).

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Two-Drug Combination for HCV Retreatment

Poordad F, Pol S, Asatryan A, et al. MAGELLAN-1, Part 2: glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic hepatitis C virus genotype 1 or 4 and prior direct-acting antiviral treatment failure. *J. Hepatol.* 2017 66, S83–S84.

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The fixed dose combination of glecaprevir/pibrentasvir (GLE/PIB) was recently approved by the US FDA for the treatment of most populations with chronic HCV genotypes 1-6, including eight weeks of therapy for all noncirrhotic, treatment-naïve patients, regardless of genotype. Another potential advantage of this combination is the improved resistance profile of both components. Glecaprevir (GLE) is a next-generation NS3 protease inhibitor with enhanced GT3 activity and a high barrier to resistance with activity against common GT1 NS3 RASs such as R155K and variants at position D168.¹ Pibrentasvir (PIB) is a next-generation NS5A inhibitor that also possesses a high barrier to resistance and is active in vitro (< 10-fold shift in activity) against all single position NS5A RASs (including Y93H) in all genotypes.¹

The MAGELLAN-1 study evaluated the efficacy of G/P in DAA experienced patients and was conducted in two parts. Part 1 of the study evaluated 12 weeks of G/P at different doses and with/without RBV.² The study will not be reviewed in detail here, but a modified intention to treat analysis (mITT) showed SVR12 of ≥ 95% for all treatment regimens. The two virologic failures did have baseline NS5A resistance, in one case in combination with NS3 resistance.

Part 2 of the MAGELLAN-1 study evaluated 12 or 16 weeks of G/P in GT1 or four DAA-



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experienced patients with or without compensated cirrhosis. Compared to part 1, part 2 is more clinically relevant as the durations and regimens evaluated are reflected in the currently approved product label.

Of the 91 patients enrolled, the majority were male (70%) and of white race (76%). Forty-four were randomized to 12 weeks of G/P and 47 to 16 weeks. Within the 12-week arm, 34% had cirrhosis and 98% were GT1 (80% GT1a). In the 16-week arm, 26% had cirrhosis and 94% were GT1 (68% GT1a). Treatment history was evenly distributed across the two arms with about 1/3 of patients previously treated within each of the following groups: NS3 PI alone, NS5A inhibitor alone, and both NS3 plus NS5A treated. NS5A RASs alone or in combination with NS3 RASs were present in majority of patients in both arms (12 week: 55% and 11%, respectively; 16 week: 52% and 9%, respectively).

Overall SVR12 was 89% (39/44) in the 12-week arm and 91% (43/47) in the 16-week arm. No patient was lost to follow-up, so all non-SVR were virologic failures (12 week: one breakthrough and four relapses; 16 week: four breakthrough). Prior DAA exposure by drug class appeared to predict treatment outcomes, with no failures in patients only exposed to NS3 PIs previously. Patients previously exposed to both NS3 and NS5A drugs had the lowest SVR with both durations (79% with 12 weeks, 81% with 16 weeks). Responses in patients only exposed to NS5A inhibitors seemed to improve with a longer duration of therapy; 88% with 12 weeks and 94% with 16 weeks. It should be emphasized that due to the relatively small number of patients in each duration, when broken down by prior drug exposure, no statistically significant differences between groups could be determined. A similar trend was observed when baseline RAS instead of prior drug exposure was used; particularly for patients with only baseline NS5A RASs SVR improved with longer duration (83% 12 weeks vs 96% 16 weeks).

References:

1. Ng T, Lu L, Reisch T, et al. [Resistance selection using glecaprevir and pibrentasvir in replicons of major hepatitis C virus genotypes](#). *J Hepatol*. 66, S324 (2017).
2. Poordad F, Felizarta F, Asatryan A, et al. [Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment](#). *Hepatology*. 2017 Aug;66(2):389-397.

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Investigational Triple-Drug Combination for HCV Retreatment

Wyles D, Wedemeyer H, Ben-Ari Z, et al; C-CREST Part C and C-SURGE Investigators. Grazoprevir, ruzasvir, and uprifosbuvir for HCV after NS5A treatment failure. *Hepatology*. 2017 Jul 7.



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Until recently, proven retreatment options have been lacking for patients failing DAA-based therapy for HCV. In particular, retreatment of patients with HCV drug resistance displayed an increased risk of retreatment failure when cross-resistant drugs were used with only two mechanisms of action (eg, NS5B nucleoside plus NS5A inhibitor).¹ In theory, combining multiple mechanisms of action, including the use of new drug classes, as well as using inhibitors with improved resistance profiles, could lead to enhanced cure rates for these difficult-to-treat populations. The coformulated combination of uprifosbuvir (an NS5B nucleoside inhibitor), grazoprevir (NS3 PI), and ruzasvir (NS5A inhibitor) possesses these characteristics and was evaluated for HCV retreatment in two phase 2 studies. The C-SURGE study evaluated this combination in patients with genotype 1 infection who had failed prior HCV treatment including an NS5A inhibitor. C-CREST part C specifically evaluated retreatment of patients with genotypes 1-3 who failed short-course therapy with eight weeks of uprifosbuvir, and grazoprevir plus either elbasvir or ruzasvir in the C-CREST



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part A study. In the C-SURGE study, patients were randomized to 16 weeks plus RBV (weight-based) or 24 weeks of treatment. In C-CREST part C all patients received open-label treatment with 16 weeks plus weight-based RBV.

In the C-SURGE study (n=93) — 86% genotype 1a, 43% with cirrhosis, 84% with NS5A RASs and 63% with NS3 RASs — the prior treatment regimens were ledipasvir/sofosbuvir (76%) and elbasvir/grazoprevir (24%). Forty-four patients were randomized to 16 weeks plus RBV and 49 patients to 24 weeks. In C-CREST part C (n = 24), 58% were genotype 2 and 33% were GT3. No patients had cirrhosis (which was an exclusion criterion for C-CREST part A). A total of 83% had NS5A RASs at baseline across both studies.

Efficacy was extremely high in both studies. SVR12 was achieved in 92/93 subjects in C-SURGE; 43/44 (98%) with 16 weeks + RBV and 44/44 with 24 weeks. There were no virologic failures, with the lone non-SVR occurring in a patient who withdrew from study at day 3 of dosing. In C-CREST part C, SVR12 was achieved by 96% of patients (23/24); again no virologic failures were seen, with the lone non-SVR being a GT2 patient who dropped out after a single dose of study medication. Obviously, with such a high SVR in both studies and no virologic failures, no baseline characteristics — including cirrhosis or resistance — adversely impacted responses. The regimen was well tolerated, with most side-effects being mild and/or attributable to RBV.

While these results are extremely impressive and highlight the efficacy of three DAA combinations with improved resistance profiles in retreatment of HCV infection with resistance, 16 weeks with RBV or 24 weeks of therapy may not be competitive given other options that only require 12 weeks of therapy. Additional studies are needed with this regimen in this population for shorter durations without RBV.

References:

1. Lawitz E, Flamm S, Yang JC, et al. [Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks](#) [EASL abstract O005] *J Hepatol.* 2015;62(1) suppl.

KEY TAKEAWAYS

- While therapeutic regimens are potent, patients who fail DAA therapy are likely to develop resistance to NS5A inhibitors and/or NS3 inhibitors if included in the initial regimen.
- NS5A RASs persist for prolonged periods of time after selection, while NS3 RASs tend to revert to wild type.
- New retreatment approaches based on two and three drug combinations with improved resistance profiles are highly efficacious for retreatment despite the presence of resistance; however, two drug class combinations should not be used to retreat patients previously exposed to both drug classes.

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