



eViralHepatitis Review VOLUME 4, ISSUE 1

NEW HCV DAA REGIMENS, RETREATMENT, AND OPTIMIZING TREATMENT OF GENOTYPE 2/3 INFECTION



In this Issue...

Despite the great success of new direct acting antiviral (DAA) regimens in treating the majority of patients with HCV, several important populations do not as yet have well-defined, highly efficacious treatment approaches. In this issue we review some of the recent investigations reporting on:

- Sofosbuvir plus daclatasvir for patients infected with genotype 3 HCV
- Sofosbuvir plus ribavirin and interferon for patients with genotype 3 infection and cirrhosis
- Three phase 3 studies of grazoprevir plus elbasvir – a new DAA regimen for GT1 (and potentially GT4 and 6), as well as for patients with end-stage renal disease
- Retreatment of patients who have failed sofosbuvir plus ledipasvir

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Evaluate the current treatment options for patients with GT2 and 3 HCV infection, including those with cirrhosis and prior treatment failure.
- Discuss phase 3 clinical trial data using the new DAA regimen of grazoprevir/elbasvir.
- Describe the limitations in currently available retreatment options for patients failing interferon-free DAA regimens, including the importance resistance may play in retreatment success.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

Program Information

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[Accreditation](#)
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Length of Activity

1.0 hour Physicians
1.0 contact hour Nurses

Launch Date

October 29, 2015

Expiration Date

October 28, 2017

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Program Directors

Mark S. Sulkowski, MD

Professor of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and
Gastroenterology/Hepatology
Johns Hopkins University School of
Medicine
Baltimore, Maryland

Raymond T. Chung, MD

Director of Hepatology and Liver Center
Vice Chief, Gastroenterology
Kevin and Polly Maroni Research
Scholar
Massachusetts General Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Julie McArthur, MS, CRNP

Adult Nurse Practitioner
Division of Infectious Disease
Johns Hopkins University School of
Medicine
Baltimore, Maryland

GUEST AUTHOR OF THE MONTH

Commentary:



David L. Wyles, MD
Associate Professor of
Medicine
Division of Infectious
Diseases
University of California San
Diego
San Diego, CA

Guest Faculty Disclosures

David L. Wyles, MD has indicated that he has received grant/research funding from AbbVie, Bristol Myers Squibb, Gilead, and Merck. He has served as a consultant/advisor for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.

Unlabeled/Unapproved Uses

David L. Wyles, MD has indicated that there will be references to the use of grazoprevir/elbasvir for the treatment of HCV infection – this combination is not currently FDA approved for the treatment of HCV infection and still considered investigational.

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COMMENTARY

EDITOR'S NOTE: To improve readability, the commonly accepted abbreviations for HCV antiviral agents are used throughout this issue. These include:

SOF = sofosbuvir
DCV = daclatasvir
RBV = ribavirin
PEG = pegylated interferon
LDV = ledipasvir
GZP = grazoprevir
EBR = elbasvir
3D regimen = paritaprevir/ritonavir/ombitasvir plus dasabuvir

Other abbreviations include:

GT = genotype
RAVs = resistance-associated variants

While the arrival of DAA therapies has revolutionized HCV treatment, populations remain in which treatment results are less than optimal. In particular, patients with — GT3 infection (especially those with cirrhosis), those with ESRD, and those who have failed a treatment course with a DAA regimen — are all groups that remain in need of improved HCV therapeutic approaches. As new treatment regimens for HCV are approved, it will be important to evaluate how those regimens address the needs of these populations.

Genotype 3 (GT3) HCV infection is associated with hepatic steatosis and an accelerated disease course and remains the primary genotype with less than optimal treatment approaches despite the arrival of sofosbuvir.¹⁻⁴ The ALLY-3 study by Nelson et al provided the first phase 3 trial data of the combination of sofosbuvir (SOF) plus daclatasvir (DCV) in patients with GT3 infection. While the responses in this study demonstrate that SOF/DCV for 12 weeks is an excellent option for patients without cirrhosis, it did not perform better than the previously accepted standard of SOF/RBV for 24 weeks in those with cirrhosis.⁴ Based on these data, SOF/DCV for 12 weeks should be the preferred initial treatment option for those with GT3 infection without cirrhosis.⁵ This approach provides the advantage of a shorter treatment duration and removal of RBV from the regimen.

However, critical questions remain around the treatment of patients with GT3 who have cirrhosis. Foremost among them is, what is the optimal approach in patients with cirrhosis? Specifically, what role does the addition of RBV and/or extension of treatment duration play in developing an effective SOF/DCV-based regimen for patients with GT3 who have cirrhosis? Those questions remain to be answered. Based on the BOSON study (reviewed herein), the treatment approach best supported by clinical trial data is pegylated interferon added to sofosbuvir plus ribavirin for 12 weeks. This regimen was superior to SOF/RBV for 16 or 24 weeks in all groups of patients with GT3 infection and is now recommended in the latest version of treatment guidelines.⁵

A collection of phase 3 studies using the DAA regimen of grazoprevir/elbasvir (GZP/EBR) offers insight into how it may be used following the anticipated regulatory approval in early 2016. This regimen consists of fixed dose combination taken once daily. In the treatment-naïve study (C-EDGE Naïve – reviewed in this issue), 12 weeks of this combination without RBV performed well — particularly in those with cirrhosis. However, similar to other PI based DAA regimens, there appeared to be a drop off in responses in those with GT1a, especially if baseline NS5A RAVs (baseline resistance associated variants) were present. Since an arm with ribavirin (RBV) was not included, it is impossible to know whether its addition will improve response; it is tempting to speculate that it might based on data from the 3D regimen with or without RBV in GT1a patients.⁶ The treatment experienced study (C-EDGE Experienced, also reviewed herein) presented at the 2015 International Liver Congress suggested that extension of therapy to 16 weeks with the addition of RBV may address the negative impact of baseline NS5A RAVs. However, this needs to be evaluated in a larger number of patients. Additionally, these data suggest that 16 weeks of therapy with RBV is needed for optimal treatment of patients with cirrhosis

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who did not respond to previous therapy. Combined, these data bring up the intriguing question whether baseline NS5A resistance testing should be performed before embarking on a treatment course using this regimen.

The C-SURFER study presented at the Liver Congress provided valuable data on the use of GZP/EBR in people with ESRD infected with HCV. Given the currently limited treatment options for this population with little trial data to support their use, the approval of this regimen will provide a welcomed additional treatment option addition. In my opinion, the most important aspect for this regimen is that it appears that RBV is not necessary for patients with GT1a who have ESRD to achieve optimal responses. Why would this requirement be different in those with ESRD compared to treatment naïve patients? While possible explanations include a lower baseline viral load in those on hemodialysis or altered drug pharmacokinetics in those with ESRD, such answers at this time remain purely speculative.

Though a small percentage of patients, those who have failed an initial DAA treatment, represent a group often in urgent need of therapy due to advanced liver disease and an area where there is little data to guide retreatment approaches. In the first retreatment study of patients who failed an initial course of sofosbuvir plus ledipasvir Lawitz et al report somewhat discouraging results for retreatment with 24 weeks of the same regimen. This study again highlighted the increasing importance of NS5A resistance in predicting treatment response in certain populations — including those with prior NS5A exposure. While predictive of outcomes, the main limitation to the clinical utility of resistance testing is the lack of proven retreatment options that do not contain a cross-resistant drug.

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ALLY-3: SOFOSBUVIR PLUS DACLATASVIR FOR GENOTYPE 3

Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology*. 2015 Apr;61(4):1127–35.

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With the advent of multiple new DAA regimens for genotype 1 HCV infection, genotype 3 (GT3) infection has now emerged as the most difficult to treat, particularly in people with cirrhosis.¹⁻³ Regimens available for GT3 infection have included sofosbuvir (SOF) plus ribavirin (RBV) for 24 weeks or SOF plus pegylated interferon (PEG)/RBV for 12 weeks. However, SOF plus RBV for 24 weeks was recently removed from guideline recommendations because of its high cost and poor efficacy in patients with cirrhosis. While it appears more efficacious in patients with difficult to treat genotype 2 and 3, the



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added side effects and medical contraindication, along with poor patient acceptance of an interferon-based regimen, limit the utility of PEG/RBV plus SOF (see BOSON study discussion below).⁴ The combination of sofosbuvir, a potent pan-genotypic NS5B nucleotide inhibitor, plus daclatasvir, a NS5A inhibitor with enhanced non-GT1 activity, was shown in preliminary phase 2 studies to have excellent efficacy against GT3 HCV infection when given for 24 weeks.⁵

To further explore the use of this DAA combination in GT3 HCV infection, the open-label phase III ALLY-3 study evaluated SOF 400mg QD plus DCV 60 mg QD for 12 weeks in patients who were treatment naïve (n = 101) and patients with HCV mono-infection who were treatment experienced (n = 51). Treatment experienced patients consisted primarily of interferon/RBV failures (87%), with the remaining seven patients having failed SOF or a cyclophilin inhibitor-containing treatment regimen. Notably, 21% of patients had cirrhosis, including 19% who were treatment naïve and 25% who were treatment experienced. Treatment was well tolerated, with rapid HCV RNA suppression on therapy. No viral breakthroughs on therapy were seen, and only one patient had low-level, detectable HCV RNA (53 IU/mL) at the end of treatment.

The primary endpoint of the study was SVR12, which was achieved by 90% and 86% of patients in the treatment naïve and experienced groups, respectively. The most striking difference in SVR12 rates was seen when comparing patients with and without cirrhosis. Overall, 96% of patients without cirrhosis and 63% with cirrhosis attained SVR12; this trend was preserved in patients who were treatment naïve (97% vs 58%) and treatment experienced (94% vs 69%). Other typically negative predictors of SVR such as IL28B status or baseline HCV RNA did not appear to have a significant impact on treatment success. Conversely, baseline resistance associated variants (RAVs), particularly Y93H, did appear to affect response. While only 13 (9%) of those sequenced harbored the Y93H RAV at baseline, the SVR12 rates were 67% (6/9) and 25% (1/4) in patients without and with cirrhosis, respectively. While definitive conclusions cannot be drawn from the small numbers, this trend is consistent with other data suggesting an impact of baseline NS5A RAVs.^{6,7}

Based on these data, SOF/DCV for 12 weeks without RBV becomes an attractive option for non-cirrhotic patients with GT3. Indeed, DCV was recently approved in the US for use in GT3 HCV infection, and recent guidelines recommend this 12 week treatment approach for patients without cirrhosis.^{8,9} Perhaps more important, the ALLY-3 study demonstrates that 12 weeks of SOF plus DCV without RBV is not optimal for patients with cirrhosis. Although responses were similar to those in patients with cirrhosis treated with 24 weeks of SOF plus RBV, a 60% SVR12 rate is no longer acceptable.³ Options for patients with cirrhosis included SOF plus PEG/RBV for 12 weeks or extension of SOF plus DCV to 24 weeks with the addition of RBV (particularly for patients who were treatment experienced).^{4,9} The recommendation for SOF plus DCV is based on limited, largely anecdotal experience and extrapolation from other DAA regimens where extension to 24 weeks and the addition of RBV appear to improve response in cirrhotic patients.⁹ A study is underway with SOF plus DCV evaluating the addition of RBV with 12 or 16 week durations in patients with GT3 who have cirrhosis.

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BOSON – SOFOSBUVIR PLUS PEGLYLATED INTERFERON PLUS RIBAVIRIN FOR GT2/GT3

Foster GR, Pianko S, Brown A, et al. Efficacy of Sofosbuvir Plus Ribavirin With or Without Peginterferon-alfa in Patients With HCV Genotype 3 Infection and Treatment-Experienced Patients with Cirrhosis and HCV Genotype 2 Infection. *Gastroenterology*. 2015 Aug..

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Preliminary data from the LONESTAR-2 study, which evaluated pegylated interferon (PEG) and ribavirin (RBV) plus sofosbuvir (SOF) for subjects with genotype 2 (GT2) and genotype 3 (GT3) suggested improved SVR rates could be obtained — particularly in patients with hard to treat conditions, such as those with cirrhosis who had failed prior treatment.¹ To better define optimal treatment approaches in these patients, the open label BOSON study enrolled treatment experienced GT2 patients with cirrhosis as well as treatment naïve and experienced patients with GT3. For GT3, patients with cirrhosis were capped at 50% of the population, and patients who had stopped prior therapy because of an adverse event were not included in the study. Patients were randomized 1:1:1 to treatment with 1) SOF plus RBV for 16 weeks, 2) SOF plus RBV for 24 weeks, or 3) SOF plus PEG/RBV for 12 weeks stratified by genotype (GT2 vs. GT3); for patients with GT3, additional stratification by treatment history and cirrhosis status was carried out. RBV dosing was weight-based, and pegylated interferon α -2a was dosed at the standard 180 μ g weekly. In total, 592 patients were enrolled and started on study treatment. The breakdown by genotype was 48 (8%) GT2 and 544 (92%) GT3. All patients with GT2 patients had cirrhosis and 31% of those with GT3 patients had cirrhosis.

Treatment efficacy was similar in GT2 patients across the 3 regimens with SVR12 rates of 87%, 100%, and 94%, respectively with 16, 24, and 12 week treatments. However, given the small number of patients with GT2 allocated to the individual study regimens, firm conclusion on differences in efficacy between the regimens cannot be made based on this study. It is perhaps notable that the two patients with virologic failure were randomized to the 16 week SOF plus RBV arm.

In patients with GT3, a clear difference in treatment efficacy was seen between the regimens in the combined population as well as in key subgroups. Overall, 71%, 84%, and 93% achieved SVR12 after treatment with the 16, 24, and 12 week regimens, respectively. Importantly, the 12 week SOF plus PEG/RBV regimen was significantly better than either 16 ($P < .001$) or 24 ($P = .008$) weeks of SOF plus RBV. Among the key subgroup of patients with GT3 who had cirrhosis, SVR12 was achieved in 51% ($n = 57$; 95% CI 37% - 64%), 79% ($n = 56$; 95% CI 66% - 88%), and 88% ($n=58$; 95% CI 77-95%) of patients, respectively. Corresponding to the difference in SVR seen, relapse rates were higher in those treated with the 16 or 24 week regimens (28% and 14%, respectively) compared to viral relapses in the 12 week group (5%). In multivariable regression analysis, only cirrhosis status was significantly associated with response when 12 weeks of SOF plus PEG/RBV was used (OR 4.59 for relapse in cirrhosis vs no cirrhosis, $P = .0361$).

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Importantly, serious adverse events and treatment discontinuation were low and no more frequent in the interferon arm (1%-2% for all arms).

Results from the BOSON study provide clarity on the relative efficacy of treatments for GT3 and treatment experienced patients with GT2 who had cirrhosis. Clearly, these results have had a significant impact on treatment recommendations, which now favor SOF plus PEG/RBV over SOF/RBV for all patients with GT3 (3). What remains to be seen is whether patient and provider reluctance to use interferon severely limits the applicability of these results to clinical practice. The arrival of daclatasvir in the US adds another option, though optimal approaches with SOF plus DCV remain to be defined for those with GT3 and cirrhosis^{2,3} (as discussed in the ALLY-3 study reviewed in this issue).

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C-EDGE NAÏVE – GRAZOPREVRIR/ELBASVIR IN TREATMENT NAÏVE PATIENTS

Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-Elbasvir combination therapy for treatment-naïve cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: A randomized trial. *Ann Intern Med.* 2015 Jul 7;163(1):1–13.

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Currently approved interferon-free HCV DAA therapies rely on an NS5B nucleotide inhibitor combined with either an NS5A inhibitor or NS3 protease inhibitor, or a ritonavir-boosted NS3 protease inhibitor combined with both an NS5A inhibitor and an NS5B non-nucleoside inhibitor. While treatment responses with these options are generally excellent, additional regimens may potentially reduce drug costs and improve access while also addressing certain unique populations that lack optimal options with the currently approved DAAs.

Grazoprevir (GZP) is a next generation NS3 protease inhibitor with a higher resistance barrier and expanded nongenotype 1 activity compared to currently available protease inhibitors.¹ Elbasvir (EBR) is a potent NS5A inhibitor with pangenotypic activity and improved in vitro activity against select NS5A RAVs (baseline resistance associated variants) such as L31M, Q30H in GT1a and L31V in GT1b.^{2,3} However, variants such as L31V in GT1a and Y93H result in large fold change increases in EBR EC50 in vitro.³ A fixed dose combination of GZP 100 mg with EBR 50 mg (GZP/EBR) is available and dosed once daily. This combination was evaluated in a phase 2 study of treatment naïve patients without cirrhosis, including those with HIV-1 coinfection. SVR12 rates ranged from 87%-97% with no apparent impact of RBV.⁴

Based on these results, this phase 3 randomized, placebo controlled study of the daily GZP/EBR fixed dose combination for treatment naïve patients with GT1, 4, or 6 with or without compensated cirrhosis was conducted. During screening, patients without -GT1 were capped at 15% and those with cirrhosis were limited to 20% of the population. At entry, subjects were randomized 3:1 immediate GZP/EBR or placebo; subjects initially



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receiving placebo rolled over to an open-label treatment phase 14 days after completing the placebo phase of the study. Among the 421 patients randomized, 316 received immediate GZP/EBR and 105 placebo. The two groups were well balanced, with the overall population being 46% female and 18% black, with 22% having cirrhosis. Patients with genotype 1 made up 91% of the study population; of those, 55% had GT1a. The primary endpoint was SVR12.

Among patients with GT1, the SVR12 rate was 95% overall, including 92% (CI: 86%-96%) in GT1a and 99% (CI: 95%-100%) in GT1b. In contrast, GT1 SVR12 rate did not appear different between patients with cirrhosis (97%; CI 90%-100%) and those without cirrhosis (94%; CI 90%-97%) patients. GT4 efficacy was excellent at 100% in 18 patients, while the SVR12 rate was 80% (8/10) in patients with GT6. There were 13 virologic failures in the study, including 10 patients with GT1a and two with GT6; only one patient with GT1b experienced virologic failure.

Baseline NS5A RAVs were detected in 12% (n = 19) of patients with GT1a and had a large impact on SVR. Only 58% (11/19) with baseline NS5A RAVs achieved SVR12, compared to 99% (133/135) of those without RAVs. Higher-fold change RAVs, arbitrarily set at > five-fold shift in EBR activity, appeared to account for most of this effect, with an SVR12 rate of only 22% (2/9) in those with high-fold change RAVs.

Tolerability of the regimen was excellent, with no significant differences from placebo. Treatment discontinuations because of adverse events were 0.9% in both active treatment and placebo arms.

The results of the C-EDGE treatment naïve study support the safety and efficacy of GZP/EBR in GT1, with the results in patients with cirrhosis being particularly encouraging. Despite the excellent overall results, the data on the impact of baseline NS5A RAVs in GT1a subjects raises some important questions. While NS5A RAVs are not particularly prevalent (10%-15%), given the substantial negative impact on SVR12 rates in GT1a, patients' baseline resistance testing may be warranted. Optimal treatment approaches with GZP/EBR in treatment naïve patients with baseline NS5A RAVs are yet to be determined. Treatment with GZP/EBR for 16 weeks with RBV appeared to negate the impact of baseline NS5A RAVs in a small number of treatment experienced patients (see C-EDGE experienced study discussed below).⁵

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C-EDGE EXPERIENCED: GRAZOPRE VIR/ELBASVIR IN TREATMENT EXPERIENCED PATIENTS

Kwo P, Gane E, Peng C-Y, et al. P0886 : Efficacy and safety of grazoprevir/elbasvir +/- RBV for 12 weeks in patients with HCV G1 or G4 infection who previously failed peginterferon/RBV: C-edge treatment-experienced trial. *J Hepatol*. 2015 Apr;62, Supplement 2:S674–5.

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In a companion study, the C-EDGE experienced study evaluated the same fixed dose combination of GZP/EBR in HCV treatment experienced patients with and without cirrhosis. Preliminary data supporting this study came from the phase 2 C-WORTHY study cohorts evaluating treatment experience null responder patients with or without cirrhosis.¹ The C-WORTHY cohorts enrolling treatment experienced patients evaluated 12 vs 18 weeks of GZP/EBR with or without RBV. SVR12 rates ranged from 91%-100% in the four cohorts with no clear impact of RBV, though numbers were small with 32-33 patients per arm. SVR rates were numerically higher with the 18 week treatment duration (97-100%).

This phase 3 C-EDGE treatment experienced study enrolled 420 patients with GT1, 4, or 6 who were randomized to GZP/EBR for 12 or 16 weeks with or without RBV, creating four treatment arms. Randomization was stratified by cirrhosis status and type of prior interferon failure (relapse, partial, or null response). Approximately 35% of the study population had cirrhosis, with an equal representation across the study arms. The proportion of subjects reporting black race was numerically higher in the 12 week arms (22%-23%) compared to the 16 week arms (9%-14%). Similarly, the proportion of patients with HCV GT1a was higher in the 12 week arms (58% for both) compared to the 16 week arms (46-55%). Null responders made up 43% of the treatment population.

Overall responses across the population were similar, with 92, 94, 92, and 97% of patients attaining SVR12 in the 12, 12 plus RBV, 16 and 16 plus RBV arms, respectively. However, of the 19 virologic failures (viral breakthrough, rebound, or relapse) none occurred in the 16 week plus RBV arm. As in the C-EDGE naïve study, patients with GT1a tended to have lower SVR12 rates, regardless of the treatment regimen, with the largest difference seen in those treated for 12 weeks without RBV, where SVR12 was 90% in GT1a versus 100% in GT1b. Patients with prior relapse to interferon did well, regardless of the treatment arm they were randomized to, while a trend toward improved responses in those with prior partial or null response was seen with 16 weeks plus RBV (100% SVR compared to 91% with 12 weeks RBV and 94% with 16 weeks no RBV). Again, an interesting story with regard to baseline NS5A RAVs and treatment responses emerged: pretreatment RAVs were detected in 14% (31/223) of patients, and the SVR12 in those with NS5A RAVs was 68% (21/31) compared to 99% (190/192) in those without. Importantly, all the failures in patients with GT1a with baseline RAVs were in those with variants that conferred a > five-fold shift in EBR potency in vitro.

Treatment was well tolerated, with some of the expected side effects of RBV being more common in those arms. Fatigue and nausea were reported more frequently in the 12 and 16 week RBV arms (fatigue 27% and 30%, respectively, nausea 14% and 17%) compared to non-RBV containing arms (fatigue 16%-19% and nausea 4%-9%). Anemia adverse events (Hgb < 10.0 g/dL) were also more common in the RBV-containing arms (9-21%) compared to none in the RBV-free arms.

Reference

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C-SURFER: GRAZOPRE VIR/ELBASVIR IN ESRD.

Roth D, Nelson D, Bruchfeld A, et al. LP02 : C-surfer: grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease. *J Hepatol*. 2015 Apr;62, Supplement 2:S263–S264.

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Treatment of HCV in patients with end-stage renal disease (ESRD) with currently approved DAA regimens is difficult due to the unknown safety profile of sofosbuvir in this population and the need to use RBV in GT1a patients with the 3D regimen of paritaprevir/ritonavir/ombitasvir plus dasabuvir.¹⁻³ Given the high prevalence of HCV in those on hemodialysis and possible association of HCV in the development of renal disease in patients with diabetes, improved therapeutic approaches are needed.^{4,5} Both components in the grazoprevir/elbasvir fixed dose combination (GZP/EBR) are hepatically metabolized and eliminated in the feces; this, combined with the potential to use this combination without RBV, makes it a potentially attractive option for patients with HCV and ESRD.

The C-SURFER study evaluated GZP/EBR in 224 HCV GT1 patients with stage 4 (GFR 15-29 mL/min) or 5 (GFR < 15 mL/min or on hemodialysis) chronic kidney disease (CKD). Patients were randomized 1:1 to immediate (n = 111) or deferred therapy (n = 113) with 12 weeks of GZP/EBR without RBV. Both treatment naïve and experienced patients were enrolled, including those with compensated cirrhosis. The demographics of the patients enrolled tended to reflect those of persons at increased risk for CKD, including 46% African American and 34% with diabetes. HCV-related characteristics included 52% GT1a, 80% treatment experienced and 6% with cirrhosis; 76% were on hemodialysis in the combined study population.

Excellent results in the immediate treatment arm were seen with 94% (115/122) SVR12 rate including a 99% (115/116) SVR12 rate for a per protocol analysis in which those who did not complete the study were censored. The six patients censored included loss to follow-up (n = 2), study withdrawal (n = 3) and one patient death not considered related to study drug. The lone viral failure was a HCV relapse in a patient with GT1b who did not have cirrhosis. Obviously, given the high SVR12 rate with a single virologic failure, all patient subgroups had a high SVR rate. In comparison with the placebo group, treatment was well tolerated, and all adverse event (AE) rates were lower than or equal to those in the treatment group. There were no discontinuations due to AEs; three deaths occurred in the placebo group vs one in the active treatment arm.

Based on this phase 3 study, GZP/EBR appears to be an efficacious and well tolerated HCV treatment option for patients with ESRD. In particular, the high SVR12 rate in subjects with GT1a without the use of RBV is a major plus for use of this regimen in those with ESRD where RBV dosing and tolerance remain difficult to manage.

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RETREATMENT OF SOF/LDV FAILURES

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. *J Hepatol*. 2015 Apr;62, Supplement 2:S192.

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Effective approaches to retreatment of patients who fail potent, interferon-free DAA regimens have not been established. Data from an initial study demonstrated that retreatment of SOF failure (n = 51) with SOF/LDV for 12 weeks with RBV was highly efficacious.¹ In that study, 98% of patients attained SVR12 on retreatment, including 50/50 with GT1 infection. The sole retreatment failure was a woman with GT3 HCV.

Whether patients who fail the more potent combination of SOF/LDV can be effectively retreated with an extended duration of the same regimen is unknown. The 1118 study investigators addressed this question in an open-label retreatment study of 41 SOF/LDV failures by treating patients with 24 weeks of SOF/LDV therapy.

The retreatment population was predominantly male (83%), with 24% black/African American and 46% having cirrhosis. As expected given their prior treatment failure with exposure to LDV, 79% had NS5A RAVs on entering the retreatment study. The majority had GT1a (83%) and had failed eight weeks (73%) of SOF/LDV previously. On treatment viral responses were consistent with prior studies of SOF/LDV, with 95% of patients having an HCV RNA < 25 IU/mL at week 4; all patients had undetectable viral loads at the end of treatment (except for the woman with GT3 infection). Following completion of therapy, 11 viral relapses occurred, bringing the SVR12 rate down to 71%.

Presence or absence of baseline NS5A resistance correlated most closely with treatment outcomes, with 100% of patients without resistance (n = 11) at entry achieving SVR12. The SVR12 rate in those with baseline resistance was only 60% (18/30). Though numbers were very small, the specific NS5A RAV present at baseline also appeared to affect treatment response – in particular, the high-fold change resistant variant Y93H or Y93N present at baseline resulted in only a 33% (2/6) SVR12 rate. Following retreatment failure, 25% of patients (3/12) had the S282T resistance mutations in NS5B, an infrequently found resistance mutation that was seen in < 1% of patients initially treated with this regimen.²

Based on these data, it is clear alternative retreatment strategies are needed for SOF/LDV failures. While the absence of baseline NS5A resistance may be useful in predicting which patients can be retreated with SOF/LDV, those results would need to be replicated in a larger study before the approach could be routinely recommended.

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KEY TAKEAWAYS

- Sofosbuvir plus daclatasvir is a good treatment option for patients with GT3 who do not have cirrhosis, while available data indicate the best response for those with cirrhosis requires interferon with SOF/RBV.

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- Grazoprevir/elbasvir is an efficacious regimen for GT1 HCV, infection but questions remain around duration and the use of RBV in patients with GT1a who have baseline NS5A resistance.
- Patients failing SOF/LDV cannot simply be retreated with a longer course of the same medications – particularly if they have NS5A resistance, as most patients will after failing an NS5A containing regimen.

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