Direct-Acting Antiviral Agents for Chronic Hepatitis C Infection

Preliminary Scan Report #1

May 2018

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This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.

Objective

The purpose of this literature scan is to preview the volume and nature of new research that has emerged since the last full review on this topic. The literature search for this scan focuses on new randomized controlled trials and comparative effectiveness reviews, as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP Participating Organizations agreed to proceed with a full report update or other review product.

Topic History

Update #3: December 2017, searches through July 2017

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center (EPC) with input from DERP Participating Organizations, which ensure that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The EPC adapted the scope and key questions to guide this update scan:

1. In patients with any HCV genotype, what are the comparative benefits and harms of all oral regimens including 2 or more DAAs?
    a. Head-to-head comparisons of different DAA regimens
    b. DAA regimen with vs. without ribavirin
    c. Varying durations of a DAA regimen
2. What are the comparative benefits and harms of DAA regimens for subpopulations of patients with the hepatitis C virus (i.e., disease stage based on fibrosis scales or presence of cirrhosis, prior treatment with interferon or DAAs, polymorphisms measured at baseline, initial viral load, posttransplant or substance abuse)?
    a. Are there differences in rates of adherence or persistence with specific add-on drugs or regimens?
    b. Are there differences in the risk of developing drug resistance?
3. What evidence supports a correlation between sustained virologic response and long-term outcomes of mortality, cirrhosis, transplant, and hepatocellular carcinoma?

Table 1: Included drugs

Drug(s)	Trade Name	FDA Status	Approved Dose	Labeled Indications	Mechanism of Action
Glecaprevir (ABT-493)/ Pibrentasvir (ABT-530)	Mavyret™	Approved 8/3/2017	300/120 mg once daily	Indicated for CHC genotypes 1 to 6 infection without cirrhosis and with compensated cirrhosis, and for adults with genotype 1 previously treated with either an NS5A inhibitor or an NS3/4A protease inhibitor, but not both.	NS3/4A protease inhibitor/NS5A inhibitor
Sofosbuvir/ Velpatasvir/ Voxilaprevir (GS-9857)	Vosevi™	Approved 7/18/2017	400/100/100 mg once daily	Indicated for adults with CHC without cirrhosis or with compensated cirrhosis who have: genotypes 1 to 6 infection previously treated with an NS5A inhibitor or genotype 1a or 3 infection previously treated with sofosbuvir without an NS5A inhibitor.	Nucleotide analog NS5B polymerase inhibitor/NS5A inhibitor/NS3/4A protease inhibitor
Sofosbuvir/ Velpatasvir	Epclusa®	Approved 6/28/2016	400/100 mg once daily	Indicated for adults with CHC genotypes 1 to 6: without cirrhosis or with compensated cirrhosis or with decompensated cirrhosis in combination with ribavirin	NS5B inhibitor/NS5A protein inhibitor
Grazoprevir/ Elbasvir	Zepatier™	Approved 1/28/2016	100/50 mg once daily	Indicated for adults with CHC genotypes 1 or 4. Indicated for use with ribavirin in: Genotype 1a: Treatment-naïve or PegIFN/RBV experienced with baseline NS5A polymorphisms or Genotype 1a or 1b: PegIFN/RBV/PI-experienced or Genotype 4: PegIFN/RBV-experienced	NS3/4A protease inhibitor/ NS5A protein inhibitor
Daclatasvir with sofosbuvir	Daklinza™	Approved 7/24/2015	60/400 mg once daily	Indicated for use with sofosbuvir, with or without ribavirin, for CHC genotype 1 or 3 infection.	NS5A inhibitor with NS5B inhibitor
2D Regimen Ombitasvir Paritaprevir Ritonavir	Technivie ™	Approved 7/24/2015	25/150/100 mg once daily	Indicated in combination with ribavirin in patients with CHC genotype 4 infection without cirrhosis or with compensated cirrhosis.	NS5A inhibitor/NS3/4A protease inhibitor
3D regimen Ombitasvir Paritaprevir Ritonavir Dasabuvir	Viekira Pak™	Approved 12/19/2014	Ombitasvir 25/150/100 mg once daily with dasabuvir 500 mg/d	Indicated for adults with CHC genotype 1a or 1b: in genotype 1a without cirrhosis or with compensated cirrhosis in combination with ribavirin or genotype 1b with or without compensated cirrhosis	NS3/4A protease inhibitor/NS5A inhibitor + non-nucleoside NS5B polymerase inhibitor
Simeprevir with Sofosbuvir	Olysio® with Sovaldi®	Approved 11/5/2014	150/400 mg once daily	CHC genotype 1 infection in treatment-naïve or treatment-experienced patients	NS3/4A inhibitor with NS5B inhibitor
Ledipasvir/ SofosIbuvir	Harvoni®	Approved 10/10/2014	90 mg/400 mg once daily	CHC genotype 1 infection in adults; with ribavirin for treatment-naïve and treatment-experienced with decompensated cirrhosis or genotypes 1 or 4: with ribavirin for treatment-naïve and treatment-experienced liver transplant recipients with or without compensated cirrhosis or genotypes 4, 5 or 6: treatment-naïve and treatment-experienced with or without cirrhosis.	NS5A inhibitor/nucleotide analog NS5B polymerase inhibitor

Inclusion Criteria

Populations

Adults and children with HCV

Interventions

Included drug regimens (see Table 1).

- At least 2 DAAs for adults
- For children and adolescents, any approved regimen (e.g. ledipasvir/sofosbuvir or sofosbuvir with ribavirin)

Comparators

DAA regimens to be compared with:

- Other DAA regimens
- The same regimen without ribavirin
- The same regimen given for a different duration

Efficacy or Effectiveness Outcomes	*Harms Outcomes*

• Clinical outcomes, including:
  o Mortality
  o Cirrhosis
  o Liver transplantation
  o Hepatocellular carcinoma
• SVR24: in absence, SVR12
• Viral relapse or reinfection with HCV
• Serious extrahepatic manifestations, including:
  o Diabetes
  o Renal disease
  o Thyroid disease
  o Lymphoma
	• Withdrawals due to adverse events
	• Specific adverse events, including:
	  o Hematologic
	  o Dermatologic
	  o Drug interactions
	• Hepatitis B reactivation

Study Designs

- RCTs
- Non-randomized studies in children and adolescents
- Comparative effectiveness reviews
  - Good-quality, covering all or most of topic scope, and with search dates ending in the last 2 years
- *Excluded* from preliminary update scan (may be included in reports): observational (non-randomized) studies

Methods for Scan

Literature Search

To identify relevant citations, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and the Cochrane Central Registry of Controlled Trials from June 2017 through April Week 2 2018 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) to identify new drugs, new populations, and new serious harms (i.e., boxed warnings). To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), and the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm). All citations were imported into an electronic database (EndNote X8) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

Results

New Drugs

None.

New Serious Harms (i.e., Boxed Warnings)

None.

Comparative Effectiveness Reviews

None.

Randomized Controlled Trials

Trials identified since Update 3

Medline searches resulted in 120 citations, of which 8 were potentially relevant to this topic. Three were publications of new head-to-head trials (4 trials, 2 in Tam 2017), and 5 were secondary publications of trials already included in Hepatitis C reports (6 trials, 2 in Zeuzem 2018). One new trial compared the DAA regimen most recently approved, glecaprevir/ pibrentasvir, to sofosbuvir with ribavirin. Two of the secondary studies were full publications of 3 trials of glecaprevir/pibrentasvir included in abstract form in Update 3. The other 3 secondary publications reported virologic resistance data from 3 included trials of older drugs. None of the publications included trials of the other DAA regimen approved in 2017, voxilaprevir with

sofosbuvir and velpatasvir. Characteristics of the trials identified are shown in Tables 2 and 3 below, and abstracts are available in Appendix B (please see separate document).

Table 2. New head-to-head trials

Author, Year Trial name	N Duration	Population	Comparison
Toyoda, 2018 CERTAIN-2	136 8 or 12 weeks	HCV G2 patients in Japan	Glecaprevir/pibrentasvir for 8 weeks vs. 12 weeks of sofosbuvir + ribavirin
Yakoot, 2017	120 8 or 12 weeks	HCV G4 patients in Egypt	Daclatasvir/sofosbuvir for response-tailored duration vs. 12 weeks
Tam, 2017 RESCUE	82 12 or 24 weeks	HCV G1 or G4	Noncirrhotic: Ledipasvir/ sofosbuvir ± ribavirin Cirrhotic: Ledipasvir/sofosbuvir + ribavirin for 12 weeks vs. ledipasvir/sofosbuvir for 24 weeks
ACTG A5348 Study	7 12 or 24 weeks	HCV G1 with HIV coinfection	Ledipasvir/sofosbuvir + ribavirin for 12 weeks vs. ledipasvir/sofosbuvir for 24 weeks

Abbreviations: ACTG, AIDS Clinical Trials Group; HCV G1, hepatitis C virus genotype 1; HIV, human immunodeficiency virus; N, number of patients

Table 3. Secondary analyses of included primary trial publications

Author, Year Trial name	N Duration	Population	Comparison	New Data
Wyles, 2018 SURVEYOR-II	44 12 or 16 weeks	HCV G3, TE with sofosbuvir or interferon	Glecaprevir/ pibrentasvir for 12 vs. 16 weeks	Full publication of trial presented in abstract form in Update 3
Zeuzem, 2018 ENDURANCE-1	1208 patients (both trials) 8 or 12 weeks	HCV G1	Glecaprevir/ pibrentasvir for 8 vs. 12 weeks	Full publication of trials presented in abstract form in Update 3
ENDURANCE-3	12 weeks	HCV G3	Glecaprevir/ pibrentasvir vs. sofosbuvir/daclatasvir	
Bruchfeld, 2017 C-SURFER	235 12 weeks	HCV G1, stage 4-5 chronic kidney disease	Grazoprevir/elbasvir vs. placebo (immediate vs. delayed treatment)	Virologic resistance
Gane, 2017 C-WORTHY	41 12 or 18 weeks	HCV G3, noncirrhotic	Grazoprevir/elbasvir for 12 vs. 18 weeks	Virologic resistance
Schnell, 2018 GIFT-II	171 12 or 16 weeks	HCV G2 patients in Japan	2D regimen (ombitasvir/ paritaprevir/ritonavir) with ribavirin for 12 vs. 16 weeks	Virologic resistance

Abbreviations: HCV G1, hepatitis C virus genotype 1; N, number of patients

Summary

Since the Update 3 report we have identified no newly approved drugs or formulations, serious harms, or comparative effectiveness reviews. We found 4 new head to head trials in 3 publications, and 5 secondary analyses of 6 trials that are relevant to this DERP report topic. One new trial and 3 trials included in previous reports were of the most recently approved DAA, glecaprevir/pibrentasvir. We found no new data on the other recently approved regimen of sofosbuvir, velpatasvir, and voxilaprevir.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

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Preliminary Scan Report #1 Appendices

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APPENDIX A. TRIALS OF DIRECT-ACTING ANTIVIRAL AGENTS FOR CHRONIC HEPATITIS C INFECTION

New Head-to-Head Trials

Tam, E., et al. (2017). "Ledipasvir/sofosbuvir for treatment of hepatitis C virus in sofosbuvir-experienced, NS5A treatment-naive patients: findings from two randomized trials." Liver International(pagination).

Background & Aims: We report data from two similarly designed studies that evaluated the efficacy, safety, and optimal duration of ledipasvir/sofosbuvir (LDV/SOF) +/- ribavirin (RBV) for retreatment of chronic hepatitis C virus (HCV) in individuals who failed to achieve sustained virological response (SVR) with prior SOF-based, non-NS5A inhibitor-containing regimens. Methods: The RESCUE study enrolled HCV mono-infected adults with genotype (GT) 1 or 4. Non-cirrhotic participants were randomized to 12 weeks of LDV/SOF or LDV/SOF + RBV. Compensated cirrhotic participants were randomized to LDV/SOF + RBV (12 weeks) or LDV/SOF (24 weeks). The AIDS Clinical Trials Group A5348 study randomized genotype 1 adults with HCV/HIV co-infection to LDV/SOF + RBV (12 weeks) or LDV/SOF (24 weeks). Both studies used SVR at 12 weeks post-treatment (SVR12) as the primary endpoint. Results: In the RESCUE study, 82 participants were randomized and treated, and all completed treatment. Overall, SVR12 was 88% (72/82); 81-100% in non-cirrhotic participants treated with LDV/SOF or LDV/SOF + RBV for 12 weeks and 80-92% in cirrhotic participants treated with LDV/SOF + RBV for 12 weeks or LDV/SOF for 24 weeks. Adverse events (AEs), mostly mild-to-moderate in severity, were experienced by 78% of participants, with headache and fatigue most frequently reported. One serious AE, not related to treatment, was observed. No premature discontinuations of study drug, or deaths occurred. In the A5348 study, seven participants were randomized (cirrhotic n = 1; GT1a n = 5) and all attained SVR12, with no serious AEs or premature discontinuations. Conclusions: In this SOF-experienced, NS5A inhibitor-naive population, which included participants with cirrhosis or HCV/HIV co-infection, high SVR12 rates were achieved. Copyright (C) 2017 John Wiley & Sons A/S.

Toyoda, H., et al. (2018). "Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection." Hepatology (Baltimore, Md.) **67**(2): 505-513.

Glecaprevir (nonstructural protein 3/4A protease inhibitor) and pibrentasvir (nonstructural protein 5A inhibitor) (G/P), a coformulated once-daily, all oral, ribavirin (RBV)-free, direct-acting antiviral regimen, was evaluated for safety and efficacy in hepatitis C virus genotype 2 (GT2)-infected Japanese patients, including those with compensated cirrhosis. CERTAIN-2 is a phase 3, open-label, multicenter study assessing the safety and efficacy of G/P (300/120 mg) once daily in treatment-naive and interferon +/- RBV treatment-experienced Japanese patients without cirrhosis but with GT2 infection. Patients were randomized 2:1 to receive 8 weeks of G/P (arm A) or 12 weeks of sofosbuvir (400 mg once daily) + RBV (600-1000 mg weight-based, twice daily) (arm B). The primary endpoint was noninferiority of G/P compared to sofosbuvir + RBV by assessing sustained virologic response at posttreatment week 12 (SVR12) among patients in the intent-to-treat population. SVR12 was also assessed in treatment-naive and interferon +/- RBV treatment-experienced patients with GT2 infection and compensated cirrhosis who received G/P for 12 weeks in the CERTAIN-1 study. A total of 136 patients were enrolled in CERTAIN-2. SVR12 was achieved by 88/90 (97.8%) patients in arm A and 43/46 (93.5%) patients in arm B. No patient in arm A experienced virologic failure, while 2 did in arm B. The primary endpoint was achieved. In CERTAIN-1, 100% (18/18) of GT2-infected patients with compensated cirrhosis achieved SVR12. Treatment-emergent serious adverse events were experienced by 2 patients without cirrhosis in each arm and no patient with cirrhosis. Conclusion: The results demonstrate high efficacy and favorable tolerability of G/P in GT2-infected Japanese patients. (Hepatology 2018;67:505-513). Copyright (C) 2017 The Authors. Hepatology published by Wiley Periodicals, Inc., on behalf of the American Association for the Study of Liver Diseases.

Yakoot, M., et al. (2017). "Response Tailored Protocol Versus the Fixed 12Weeks Course of Dual Sofosbuvir/Daclatasvir Treatment in Egyptian Patients With Chronic Hepatitis C Genotype-4 Infection: A Randomized, Open-label, Non-inferiority Trial." EBioMedicine **21**: 182-187.

BACKGROUND: The most recent European Association for the Study of the Liver (EASL) 2016 Guidelines on treatment of hepatitis C (HCV), allowed for shortening the course of treatment for some subsets of patients with sofosbuvir/ledipasvir and with grazoprevir/elbasvir based on cutoff baseline HCV RNA values. We hypothesized that it would be prudent to also consider an objectively assuring very rapid, on-treatment, virologic response to therapy at week 2 (vRVR) before taking the decision of shortening the treatment duration. So we planned this study to test whether a dual sofosbuvir/daclatasvir (SOF/DCV) treatment duration tailored according to achieving vRVR to 8 or 12weeks is non-inferior to the recommended fixed 12weeks course in non-cirrhotic Egyptian chronic HCV genotype-4 patients.

METHODS: The study was conducted in an outpatient setting according to a prospective, randomized, open-label, comparative, non-inferiority study design. A hundred twenty eligible, non-cirrhotic, chronic HCV patients were randomly assigned (1:1) to receive daily doses in the form of one Gratisovir 400mg table (generic sofosbuvir produced by Pharco Pharmaceuticals, Alexandria, Egypt) plus one Daktavira 60mg tablet (generic daclatasvir produced by Dawood Pharm, Egypt) for either a fixed 12weeks duration (reference group) or a response tailored duration (test group). In the test group the treatment duration was tailored according to the virus load tested by real time PCR into 8weeks for patients who had undetectable HCV RNA level in their serum by the end of the second week of treatment (vRVR)), or 12weeks for those who did not show vRVR. The primary outcome of the trial was the proportions of patients achieving SVR12 (HCV RNA below lower level of quantification at week 12 after end of treatment). The comparison between groups was based on testing the null hypothesis of inferiority of the response-tailored group with a pre-specified margin of non-inferiority (NI_{-m}) of 0.1 (10%). The protocol was registered with a WHO Clinical Trial Registration ID: ACTRN12617000263392.
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372041 FINDINGS: Starting from Jun, 5 2016, a hundred twenty eligible patients from 4 outpatient clinics in Alexandria, Egypt were randomized to either a fixed duration group (reference group: n=60 patients) or a response tailored duration group (test group: n=60 patients). During the whole period of the study, only 1 patient dropped-out from each group. Both were lost to follow-up after the 4th week's visit. Baseline characteristics in both groups were almost matching. Fifty eight out of the total 60 intention-to-treat (ITT) patients in the reference group achieved SVR12 (96.67% (95% confidence interval (CI): 88.64-99%). Whereas, 59 out of the total 60 (ITT) patients in the test group achieved SVR12 (98.33% (CI: 91.14-99.71%). The per-protocol (PP) analysis, excluding patients who dropped-out before collecting their final result, showed that 58/59 (98.31% (CI: 91-99.7%)) of patients in the reference group and 59/59 (100% (CI: 93.89-100%) of the test group achieved SVR12. Non-inferiority was declared since the upper bound of the two-sided 95% CI for the difference in proportions of SVR12 between groups (P_(reference)-P_(test)) did not exceed the specified non-inferiority margin of +0.1 (10%), both in ITT population (-1.67%, CI: -9.8%-+5.9%), and in the PP population (-1.69%, CI: -9%-+4.58%). No fatalities or serious adverse events were reported during the period of the study. Similar rates of non-serious adverse events were reported in both groups with a trend of higher incidence rate in the fixed 12weeks group; all were mild in severity.

INTERPRETATION: Shortening the duration of therapy based on observed vRVR could provide a prudent basis to avoid unnecessary long treatment courses. This could not only reduce the drug exposure and the risk of adverse drug reactions, but also cut the cost of full treatment course with such expensive medications by one third. This could economize the treatment budget at the individual out-of-pocket level as well as the public health services and insurance levels and allow for better utilization of public health resources.

Secondary Publications of Included Trials

Bruchfeld et al. (2017). "Elbasvir plus grazoprevir in patients with hepatitis C virus infection and stage 4-5 chronic kidney disease: clinical, virological, and health-related quality-of-life outcomes from a phase 3, multicentre, randomised, double-blind, placebo-controlled trial." The lancet gastroenterology and hepatology **2**(8): 585-594.

Background In the C-SURFER study, therapy with the all-oral elbasvir plus grazoprevir regimen for 12 weeks in patients with chronic hepatitis C virus (HCV) infection and stage 4-5 chronic kidney disease resulted in a high rate of virological cure compared with placebo. Here, we report sustained virological response (SVR), safety data, health-related quality-of-life (HRQOL), and virological resistance analyses in patients in C-SURFER who received immediate antiviral therapy or who received placebo before therapy. Methods In this

phase 3, multicentre, randomised, placebo-controlled study, we randomly assigned adults with HCV genotype 1 infection and stage 4-5 chronic kidney disease enrolled at 68 centres worldwide to either elbasvir 50 mg plus grazoprevir 100 mg once per day for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by elbasvir 50 mg plus grazoprevir 100 mg once per day for 12 weeks beginning at week 16 (deferred treatment group). The primary safety and efficacy endpoints for the immediate treatment group and placebo phase of the deferred treatment group have been reported previously. Here, we report safety and efficacy data for the treatment phase of the deferred treatment group, as well as HRQOL assessed using the 36-Item Short Form Health Survey for all groups, and baseline and treatment-emergent resistance-associated substitutions (RASs). SVR at 12 weeks (SVR12) was assessed in the modified full analysis set (FAS), defined as all patients excluding those who did not receive at least one dose of study drug, who died, or who discontinued the study before the end of treatment for reasons determined to be unrelated to HCV treatment. This trial is registered with ClinicalTrials.gov, Number NCT02092350. Findings Between March 30 and Nov 28, 2014, 235 patients were enrolled and received at least one dose of study drug. The modified FAS included 116 patients assigned to immediate treatment and 99 assigned to deferred treatment. 115 (99.1%; 95% CI 95.3-100.0) of 116 assigned to immediate treatment achieved SVR12 compared with 97 (98.0%; 92.9-99.7) of 99 assigned to deferred treatment. In patients with genotype 1a infections, SVR12 was achieved by 11 (84.6%) of 13 patients with detectable baseline NS5A RASs and in 98 (100%) of 98 without. HRQOL did not differ at week 12 between immediate treatment and the placebo phase of deferred treatment. Safety was generally similar between patients receiving immediate treatment and those receiving placebo in the deferred treatment group. One serious adverse event during deferred treatment (interstitial nephritis) and one during the placebo phase of deferred treatment (raised lipase concentration) were deemed related to study drug. Four patients died, one who received immediate treatment (cardiac arrest) and three who received deferred treatment (aortic aneurysm, pneumonia, and unknown cause); all four deaths were considered unrelated to study drugs. Of the three deaths in the deferred treatment group, one occurred during placebo treatment and two occurred before starting active treatment. There were no notable differences in aminotransferase elevations in the deferred treatment group compared with the immediate treatment group, and no patients in the deferred treatment group had total bilirubin elevations. Interpretation These data add to the growing body of clinical evidence for the fixed-dose combination regimen of elbasvir plus grazoprevir for 12 weeks and support use of this therapy in patients with HCV genotype 1 infection and stage 4-5 chronic kidney disease. Funding Merck Sharp & Dohme. Copyright (C) 2017 Elsevier Ltd

Gane, E., et al. (2017). "Efficacy of 12 or 18 weeks of elbasvir plus grazoprevir with ribavirin in treatment-naive, noncirrhotic HCV genotype 3-infected patients." Journal of Viral Hepatitis(pagination).

Elbasvir (EBR; HCV NS5A inhibitor) and grazoprevir (GZR; HCV NS3/4A protease inhibitor) are approved as a fixed-dose combination to treat patients chronically infected with HCV genotypes 1 and 4. During the development programme and supported by in vitro potency, the efficacy of EBR+GZR was assessed in HCV GT3-infected patients. This study's aim was to determine the efficacy and tolerability of 12 or 18 weeks of EBR+GZR with ribavirin (RBV) in treatment-naive, noncirrhotic HCV GT3-infected patients. Randomized patients received open-label EBR (50 mg once daily) + GZR (100 mg once daily) + RBV. The primary efficacy objective was to evaluate the sustained virologic response rates 12 weeks after the end of all study therapy (SVR12). SVR12 rates (95% confidence interval) were 45.0% (23.1, 68.5) and 57.1% (34.0, 78.2) after treatment with EBR+GZR+RBV for 12 weeks or 18 weeks, respectively. On-treatment virologic failure was observed in 41% (17 of 41) of patients. At virologic failure, resistance-associated substitutions (RASs) with a >five-fold shift in potency occurred in the NS3 region in six (35%) patients and in the NS5A region in 16 (94%) patients. The most common RAS at virologic failure was Y93H in NS5A which was identified in 13 of 17 (76%) patients. The efficacy of EBR+GZR+RBV was suboptimal in HCV GT3-infected patients due to a high rate of on-treatment virologic failure and treatment-emergent RASs which demonstrates an inadequate barrier to the development of GT3 resistance. However, rapid viral clearance demonstrated the antiviral activity of EBR+GZR+RBV in GT3-infected patients.clinicaltrials.gov: NCT01717326. Copyright (C) 2017 John Wiley & Sons Ltd.

Schnell, G., et al. (2018). "Resistance characterization of hepatitis C virus genotype 2 from Japanese patients treated with ombitasvir and paritaprevir/ritonavir." Journal of Medical Virology **90**(1): 109-119.

Treatment of HCV genotype (GT) 2-infected Japanese patients with paritaprevir (NS3/4A inhibitor boosted with ritonavir) and ombitasvir (NS5A inhibitor) without ribavirin for 12 weeks in the phase 2 study M12-536, and with ribavirin for 16 weeks in phase 3 study GIFT II resulted in SVR rates of 72.2% to 91.5%. Overall, 11 out of 125 patients with GT2a and 37 out of 79 patients with GT2b infection experienced virologic failure. The prevalence of baseline polymorphisms in NS3 and NS5A and their the impact on treatment outcome, as well as the development of viral resistance in GT2-infected patients experiencing virologic failure were evaluated by HCV NS3 and NS5A population and clonal sequence analyses. Baseline polymorphisms in NS3 that confer resistance to paritaprevir were rare in both GT2a- and GT2b-infected patients, while baseline polymorphisms in NS5A that confer resistance to ombitasvir were detected in 11.2% and 14.1% of the GT2a- and GT2b-infected patients, respectively. There was no significant impact of baseline polymorphisms on treatment outcome in Japanese patients. The most common treatment-emergent substitutions at the time of virologic failure occurred at amino acid positions 168 in NS3 and 28 in NS5A in both GT2a- and GT2b-infected patients. Although there was a higher rate of virologic failure in patients with GT2b infection, the resistance analyses presented in this report support the conclusion that testing for baseline resistance-associated polymorphisms is not warranted for HCV GT2-infected patients treated with a regimen of ombitasvir/paritaprevir/ritonavir + ribavirin for 16 weeks. Copyright (C) 2017 The Authors. Journal of Medical Virology Published by Wiley Periodicals, Inc.

Wyles, D., et al. (2018). "Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: a partially randomized phase 3 clinical trial." Hepatology (Baltimore, Md.) **67**(2): 514-523.

This study assessed the efficacy and safety of ribavirin-free coformulated glecaprevir/pibrentasvir (G/P) in patients with hepatitis C virus genotype 3 infection with prior treatment experience and/or compensated cirrhosis, a patient population with limited treatment options. SURVEYOR-II, Part 3 was a partially randomized, open-label, multicenter, phase 3 study. Treatment-experienced (prior interferon or pegylated interferon +/- ribavirin or sofosbuvir plus ribavirin +/- pegylated interferon therapy) patients without cirrhosis were randomized 1:1 to receive 12 or 16 weeks of G/P (300 mg/120 mg) once daily. Treatment-naive or treatment-experienced patients with compensated cirrhosis were treated with G/P for 12 or 16 weeks, respectively. The primary efficacy endpoint was the percentage of patients with sustained virologic response at posttreatment week 12 (SVR12). Safety was evaluated throughout the study. There were 131 patients enrolled and treated. Among treatment-experienced patients without cirrhosis, SVR12 was achieved by 91% (20/22; 95% confidence interval [CI], 72-97) and 95% (21/22; 95% CI, 78-99) of patients treated with G/P for 12 or 16 weeks, respectively. Among those with cirrhosis, SVR12 was achieved by 98% (39/40; 95% CI, 87-99) of treatment-naive patients treated for 12 weeks and 96% (45/47; 95% CI, 86-99) of patients with prior treatment experience treated for 16 weeks. No adverse events led to discontinuation of study drug, and no serious adverse events were related to study drug. Conclusion: Patients with hepatitis C virus genotype 3 infection with prior treatment experience and/or compensated cirrhosis achieved high SVR12 rates following 12 or 16 weeks of treatment with G/P. The regimen was well tolerated. (Hepatology 2018;67:514-523). Copyright (C) 2017 The Authors and AbbVie. Hepatology published by Wiley Periodicals, Inc., on behalf of the American Association for the Study of Liver Diseases.

Zeuzem, S., et al. (2018). "Glecaprevir-Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection." New England Journal of Medicine **378**(4): 354-369.

BACKGROUND: Glecaprevir and pibrentasvir are direct-acting antiviral agents with pangenotypic activity and a high barrier to resistance. We evaluated the efficacy and safety of 8-week and 12-week courses of treatment with 300 mg of glecaprevir plus 120 mg of pibrentasvir in patients without cirrhosis who had hepatitis C virus (HCV) genotype 1 or 3 infection.

METHODS: We conducted two phase 3, randomized, open-label, multicenter trials. Patients with genotype 1 infection were randomly assigned in a 1:1 ratio to receive once-daily glecaprevir-pibrentasvir for either 8 or 12 weeks. Patients with genotype 3 infection were randomly assigned in a 2:1 ratio to receive 12 weeks of treatment with either glecaprevir-pibrentasvir or sofosbuvir-daclatasvir. Additional patients with genotype 3 infection were subsequently enrolled and nonrandomly assigned to receive 8 weeks of treatment with glecaprevir-

pibrentasvir. The primary end point was the rate of sustained virologic response 12 weeks after the end of treatment.

RESULTS: In total, 1208 patients were treated. The rate of sustained virologic response at 12 weeks among genotype 1-infected patients was 99.1% (95% confidence interval [CI], 98 to 100) in the 8-week group and 99.7% (95% CI, 99 to 100) in the 12-week group. Genotype 3-infected patients who were treated for 12 weeks had a rate of sustained virologic response at 12 weeks of 95% (95% CI, 93 to 98; 222 of 233 patients) with glecaprevir-pibrentasvir and 97% (95% CI, 93 to 99.9; 111 of 115) with sofosbuvir-daclatasvir; 8 weeks of treatment with glecaprevir-pibrentasvir yielded a rate of 95% (95% CI, 91 to 98; 149 of 157 patients). Adverse events led to discontinuation of treatment in no more than 1% of patients in any treatment group.

CONCLUSIONS: Once-daily treatment with glecaprevir-pibrentasvir for either 8 weeks or 12 weeks achieved high rates of sustained virologic response among patients with HCV genotype 1 or 3 infection who did not have cirrhosis. (Funded by AbbVie; ENDURANCE-1 and ENDURANCE-3 ClinicalTrials.gov numbers, NCT02604017 and NCT02640157 .).