Observational Study

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Real-world observational experience with direct-acting antivirals for hepatitis C: baseline resistance, efficacy, and need for long-term surveillance

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Abstract

The aim of this study was to obtain real-world, US, observational data on the effect of baseline resistance-associated substitutions (RASs) on achieving sustained virologic response (SVR) in hepatitis C (HCV) patients treated with direct-acting antiviral (DAA) regimens; the need for long-term follow-up in post-SVR patients.

It is uncertain if the presence of RASs limits efficacy to DAAs. Once SVR is achieved, society guidelines recommend long-term surveillance for hepatocellular carcinoma in certain patients. Real-world data are limited on these topics.

Adult patients treated with DAAs at community hepatitis clinics between January 2015 and April 2017 were included in this study. Baseline resistance testing was performed before treatment. Per guidelines, post-SVR long-term monitoring was required in patients with F3 to F4 fibrosis before treatment or with elevated ALT levels (>19 U/L females; >30 U/L males).

A total of 875 chronic, mostly GT1a (60%) HCV patients were treated with an approved DAA regimen. Average baseline AST and ALT were 75 and 67 U/L, respectively, and 47% had F3 to F4 fibrosis at baseline. SVR was achieved in 863 (98.6%) patients despite a high presence of baseline RASs (61%). Long-term monitoring was required post-SVR in 539 patients (62%).

In a real-life, US cohort of HCV-infected patients, nearly all patients achieved SVR with available DAA regimens regardless of baseline RASs. Approximately two-thirds of these patients required long-term follow-up, despite viral eradication.

Abbreviations: AASLD = American Association for the Study of Liver Diseases, AGA = American Gastroenterological Association, ALD = alcoholic liver disease, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CDC = Center for Disease Control and Prevention, CI = confidence interval, DAA = direct-acting antiviral, EBR/GRZ = elbasvir/grazoprevir, EOT = end of treatment, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, IU = international units, NAFLD = nonalcoholic fatty liver disease, OBV/PTV/r + DSV = ombitasvir/paritaprevir/ritonavir plus dasabuvir, RAS = resistance-associated substitution, RBV = ribavirin, SOF + DCV = sofosbuvir + daclatasvir, SOF + SIM = sofosbuvir + simeprevir, SOF/LDV = sofosbuvir/ledipasvir, SOF/VEL = sofosbuvir/velpatasvir, SVR = sustained virologic response, US = United States.

Keywords: direct-acting antivirals, hepatitis C, real-world, resistance, sustained virologic response

1. Introduction

The hepatitis C virus (HCV) is a persistent and prevalent infection that can result in dire consequences. It is estimated that 71 million people across the globe are infected with chronic HCV.[1] In the United States, approximately 3.5 million people have HCV[2,3] and, despite major preventative and treatment initiatives, cases reported to the Centers for Disease Control and Prevention (CDC) have tripled from 2010 to 2015.[4] Americans born from 1945 to 1965 often referred to as "baby boomers," most commonly present with HCV[5] and are at a significant risk of HCV-related mortality. However, the highest overall number of new infections is now among individuals 20- to 29-year-old; this is attributed to increasing injection opioid use, which promotes transmission.[4]

The growing number of new HCV cases in the United States is a cause for concern; these patients are at an increased risk of hepatic fibrosis, cirrhosis, hepatocellular carcinoma, and death.[6] Without proper intervention, HCV mortality rates are expected

Editor: King-Wah Chiu.

RR: Speaker bureau for AbbVie and Gilead Sciences. KH: Speaker bureau for AbbVie. NA and EL: Speaker bureau, consultancy and research funding from AbbVie, Gilead Sciences and Merck & Co. The following authors have nothing to declare: FP, NL, BH, JM, JK, RM, TVF, RG, KC, LDP, JW, CL, and FR.

The authors report no conflicts of interest

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Medicine (2019) 98:26(e16254)

Received: 5 April 2019 / Received in final form: 4 May 2019 / Accepted: 6 June 2019

http://dx.doi.org/10.1097/MD.0000000000016254

to significantly increase. Fortunately, in the past decade the standard of care for HCV treatment has rapidly evolved with the approval of direct-acting antivirals (DAAs). These oral drugs target specific nonstructural proteins of the virus and disrupt viral replication and infection. The introduction of the first generation DAA regimens coincides with a decrease in HCV-related mortality between 2007 and 2013, according to a recent population-based study.[7] Treatment has now evolved to second- and third-generation DAA regimens. Virologic cure of HCV (i.e., sustained virologic response [SVR]), defined as undetectable levels of HCV RNA in the blood 12 weeks after completion of therapy[8], has reached as high as 99% with DAA therapies.[9,10] In addition to these high cure rates, second-generation DAAs offer favorable safety profiles, high-resistance barriers, and convenient dosing.[11]

One important consideration to optimal first- and some second-generation DAA use is viral resistance. The HCV virus has a high replication rate, which, combined with a fallible RNA polymerase, promotes a setting for the development of viral nucleotide mutations, commonly referred to as resistance-associated substitutions (RASs), that are the basis for resistance to DAAs.[12] Clinically relevant RASs are most commonly found within the nonstructural protein (NS)3/4A protease and NS5A; these may be preexisting but also emerge under the selective pressure of certain DAAs.[13] Specifically, the presence of NS3/4A RAS Q80K, NS5A RASs Q30, L31, and Y93 were shown to impact achievement of SVR in some genotype (GT) 1a patients treated with certain DAA regimens.[14]

Another significant clinical consideration is whether long-term monitoring is necessary after patients are cured of HCV. Encouragingly, large prospective studies have demonstrated that HCV cure is durable in >99% of patients followed up for ≥5 years, so relapse should not be expected.[8,15,16] The administration of highly effective agents combined with these enduring, long-term results will surely result in a large and expanding pool of cured HCV patients. As such, clinicians require guidance on follow-up care for patients with underlying liver disease. Practice guidelines from the American Association for the Study of Liver Diseases (AASLD)[8] and the American Gastroenterological Association (AGA)[17] advise that patients with advanced fibrosis (i.e., Metavir stage F3 or F4) before treatment and/or with elevated serum levels of liver enzymes post-SVR should undergo twice-yearly surveillance for hepatocellular carcinoma. These recommendations are largely based on expert opinion; limited real-world data are available to guide hepatologists on which post-SVR patients can be discharged from practice safely versus those that require long-term monitoring.[17] Patients with minimal-to-moderate fibrosis (F0–F2) at baseline before SVR are often discharged from the care of a liver specialist. However, a large percentage of these individuals may have elevated ALT, suggesting other risk factors for liver disease. The risk for alcohol induced liver injury, fatty liver disease, medication-related liver injury and autoimmune conditions needs to be considered before discharging a patient from follow-up care.

We conducted an observational study to gather real-world data that is currently scarce, yet important, to HCV management. The aim of this study was twofold. The first objective was to assess the impact of RASs on achieving SVR in a community population of HCV patients treated with second-generation DAA treatment regimens. The second objective was to determine the likelihood, from this same patient population, on the need for long-term monitoring in cured HCV patients based on criteria recommended in published guidelines.

2. Methods

This prospective, multicenter, observational, real-world study collected standard of care data. The testing performed on and DAA regimen administered to each patient was at the sole discretion of the treating physician. The protocol was designed in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local regulations. The protocol was approved by IntegReview, an independent institutional review board.

Between January 2015 and April 2017, patients with chronic HCV were evaluated at several community clinics, with academic oversight, in Texas. To be included in the analysis, patients had to be 18 years of age or older, HCV treatment naive or failed prior treatment and treated for a minimum of 4 weeks with a DAA regimen according to the product's package insert. Reported patient baseline characteristics were age, gender, race, and ethnicity. Disease-related characteristics that were evaluated included HCV genotype, liver fibrosis stage, prior HCV treatment status, prior liver transplant, and HCV RNA viral load, which was collected before treatment, at the end of treatment and ≥ 12 weeks after the end of treatment. Further clinical information captured were presence of diabetes, creatinine clearance and need for dialysis, coinfection with HIV, and proton pump inhibitor use. Baseline and post-SVR laboratory values analyzed included aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, hemoglobin, and hepatitis B surface antigen (HBsAg). Resistance testing via population sequencing was performed to detect the presence of RASs and assess whether they had any impact on SVR.

The methods of assessing fibrosis stage included liver biopsy, elastography, and biochemical assessments and were at the discretion of the treating physician. As this was an observational, noninterventional study, only standard of care data collection was captured.

According to the AASLD and AGA guidelines, long-term monitoring is recommended in patients with stage 3 or 4 fibrosis before treatment or with persistently elevated ALT (>19 U/L for females and >30 U/L for males) after achieving SVR.[8,17] Post hoc univariate analysis and logistic regression analysis were performed to identify baseline factors, in accordance with these guidelines, that were associated with the need for long-term monitoring. Patients treated after liver transplantation were excluded from the long-term monitoring requirement analysis because those patients would already remain in the care of a liver specialist.

Descriptive statistics were used to assess patient demographics, the prevalence of baseline resistance testing, the severity of liver fibrosis at baseline, and the percentage of patients that achieved SVR. Univariate analysis was performed using Mann–Whitney *U* tests, chi-squared tests, and Fisher exact test and determined factors associated with the need for post-SVR long-term follow-up. Logistic regression analysis evaluated the importance of these variables via the mean decrease in accuracy. All analyses were done with the statistical software R.

3. Results

A total of 875 chronic HCV patients were treated with a DAA regimen between January 2015 and April 2017 at several clinical

Table 1

Baseline patient demographics and characteristics.

Characteristics	Patients (N = 875)
Age, mean (SD)	58 (10.5)
Male, N (%)	499 (57)
Race	
White, N (%)	704 (80.5)
Black, N (%)	84 (9.6)
Other, N (%)	87 (9.9)
Ethnicity	
Hispanic, N (%)	379 (43.3)
Non-Hispanic, N (%)	496 (56.7)
Genotype	
1a, N (%)	525 (60)
1b, N (%)	192 (21.9)
2, N (%)	74 (8.5)
3, N (%)	65 (7.4)
4/5/6 multiple, N (%)	19 (2.2)
Viral load (IU/mL) , median	1,663,536
Prior HCV treatment, N (%)	219 (25)
IFN-based	160 (18)
DAA-based	59 (6.7)
Fibrosis stage	
F0, N (%)	70 (8.0)
F1, N (%)	164 (18.7)
F2, N (%)	192 (21.9)
F3, N (%)	118 (13.5)
F4, N (%)	293 (33.5)
Unknown, N (%)	38 (4.3)
Mean ALT (U/L)	75
Mean AST (U/L)	67
Mean platelet count ($10^3/\mu L$)	182
Mean hemoglobin (mg/dL)	14.0
Mean creatinine clearance (mL/min)	103.7
Diabetes, N (%)	182 (20.8)
HIV/HCV coinfected, N (%)	21 (2.4)
Use of proton pump inhibitor, N (%)	210 (24)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HCV = hepatitis C virus, IU = international units.

Table 2

Baseline resistance-associated substitutions.

Characteristics	Patients (N = 711)
≥1 RAS, N (%)	435 (61.2)
Any NS3 RAS	340 (47.8)
Any NS5A RAS	139 (19.5)
Any NS5B RAS	15 (2.1)
Type of RAS, N (%)	
NS3 Q80	248 (35)
NS5A M28	33 (4.6)
NS5A Q30	19 (2.7)
NS5A L31	18 (2.5)
NS5A Y93	26 (3.7)
Patients who did not achieve SVR, N (%)	11* (1.5)
RAS present†	6 (54.5)
No RAS	3 (27.3)
Test not performed	2 (18.2)

* Data available on 11/12 patients that did not achieve SVR.
† Q80 in 4 patients; Q80 and S556 in 1 patient; Q30 in 1 patient.
RAS = resistance associated substitution, SVR = sustained virologic response.

community sites with academic oversight. Patient characteristics at baseline are shown in Table 1. The average age was 58 years and the majority of patients were white (80%) and non-Hispanic (57%) with GT1a infection (60%). Average levels of baseline AST and ALT were elevated (75 and 67 U/L, respectively) and nearly half of the patients presented with advanced liver disease (47% with F3/F4 fibrosis at baseline).

HCV was treated using the DAA treatment regimens sofosbuvir/ledipasvir (SOF/LDV, n = 563), sofosbuvir + daclatasvir (SOF + DCV, n = 124), ombitasvir/paritaprevir/ritonavir plus dasabuvir (OBV/PTV/r + DSV, n = 84), sofosbuvir + simeprevir (SOF + SIM, n = 50), sofosbuvir plus ribavirin (SOF + RBV, n = 23), sofosbuvir/velpatasvir (SOF/VEL, n = 16), and elbasvir/grazoprevir (EBR/GRZ, n = 15). Treatment duration was 8, 12, 16, or 24 weeks based on FDA-approved labeling and depended on drug regimen, genotype, baseline viral load, and/or presence/absence of cirrhosis. Ribavirin (RBV) was prescribed to 13.7% (120/875) of patients. Treatment regimens were selected at the discretion of the physician and were not based on RAS profiles alone. SVR was achieved in 98.6% (863/875) of patients and the majority of patients (74%) were prescribed a 12-week DAA regimen. SVR rates for the various regimens were 99.4% for SOF/LDV ± RBV (560/563), 99.1% for SOF + DCV ± RBV (123/124), 95.2% for OBV/PTV/r + DSV ± RBV (80/84), 98.0% for SOF + SIM +RBV (49/50), 95.6% for SOF + RBV (22/23), 93.8% for SOF/VEL± RBV (15/16), and 100% for EBR/GRZ ± RBV (15/15).

Table 2 provides details on the 711 patients (81%) who had baseline resistance testing performed prior to current treatment; 61% (435/711) had ≥1 detectable RAS reported via commercial lab sequencing. The most commonly observed RAS was the NS3 Q80 polymorphism, which was detected in 35% (n = 248) of those tested. With regard to NS5A RASs, individual detection rates were <5% for M28, Q30, L31, and Y93. RAS data were available for 11 of the 12 non-SVR patients; baseline RASs were detected in 6 of these patients. Of these 6 non-SVR patients with baseline RASs, 5/6 had the Q80 RAS detected, half were treatment naive (n = 3) and only 1 had prior exposure to 2 DAA regimens, one of which contained an NS5A inhibitor (LDV). The presence of RASs was not linked to nonresponse to treatment with DAA regimens (Table 3). Resistance testing was performed posttreatment in 3 patients who did not achieve SVR. Of those, 1 patient exposed to SOF + SIM had no RASs detected, 1 patient exposed to SOF/LDV had NS5A L31 detected (only Q80 detected at baseline) and 1 patient exposed to OBV/PTV/r+DSV+RBV had NS5A M28, Q80 and D168 detected (only Q80 detected at baseline).

Patients achieving SVR (n = 863) were further studied to determine the need for long-term monitoring. A total of 539 (62.4%) of these patients met AASLD/AGA criteria for twice-yearly hepatocellular carcinoma surveillance, whereas 324 (37.5%) did not meet these criteria. Of the patients who required long-term monitoring, 411 (47.6%) had baseline F3 to F4 fibrosis and 128 (14.8%) had elevated ALT post-SVR without advanced fibrosis. Results of the secondary analysis (Table 4) determined that factors significantly associated with long-term monitoring included lower pretreatment platelet counts, lower pretreatment creatinine clearance, higher pretreatment AST, and those prescribed a longer (>12 weeks) DAA treatment duration (logistic regression analysis, $P < 0.05$).

4. Discussion

In real-world, community-based centers, patients treated with HCV DAA regimens (used in accordance with prescribing

Table 3

By-patient listing of patients who relapsed.

Genotype	Fibrosis	Prior treatment	Prescribed regimen	Compliance	Treatment duration	Baseline RAS
1a	F0	IFN + RBV	OBV/PTV/r + DSV + RBV	Compliant	12 wk	Q80
1a	F1	Naive	OBV/PTV/r + DSV + RBV	Noncompliant	12 wk	Q80
1a	F2	Naive	LDV/SOF	Noncompliant; undetectable at EOT; lost to follow-up	12 wk	None
1a	F2	IFN+RBV	OBV/PTV/r + DSV	Noncompliant	12 wk	Q80
1a	F4	Naive	SOF/LDV + RBV	Compliant	12 wk	Q80
1a	F4	SOF/LDV; SIM + SOF + RBV	VEL/SOF+RBV	Compliant	12 wk	Q30
1a	F4	Naive	OBV/PTV/r + DSV + RBV	Noncompliant; undetectable at EOT; lost to follow-up	24 wk	Q80; S556
1a	F4	IFN + RBV	LDV/SOF	Compliant	24 wk	None
1a	Unknown	Naive	SOF + SIM	Compliant	24 wk	None
2	F4	Naive	SOF + RBV	Compliant	12 wk	Not done
3	F4	SOF + RBV	SOF + DCV	Compliant	24 wk	Not done

DCV = daclatasvir, DSV = dasabuvir, EOT = end of treatment, IFN = interferon, LDV = ledipasvir, OBV = ombitasvir, PTV/r = paritaprevir/ritonavir, RAS = resistance associated substitution, RBV = ribavirin, SIM = simeprevir, SOF = sofosbuvir, VEL = velpatasvir.

instructions) can achieve SVR rates that approach 99%; this is comparable to results demonstrated in controlled clinical trials[9,10] and published real-world data.[18–21]

There was no consistent factor that could account for nonresponse in the small percentage of patients who did not achieve SVR. This includes the presence of RASs, which unlike other published real-world studies performed in the United States, were assessed at baseline, before initiating DAA regimens. Despite being frequently detected, RASs had very little impact on cure rates in this patient cohort. These results are also consistent with clinical trial data; Sarrazin et al performed an analysis in 2144 GT1a and 1b patients and found that baseline RASs in NS5A have minimal effects on response to LDV/SOF therapy.[14] This is also in accordance with the AASLD guidelines, which state that RAS testing alone cannot dictate patient response to DAA regimens.[22] However, it should be noted that the population studied was heterogeneous with respect to genotype and HCV regimen used and the number of patients who failed treatment was limited. Most patients were DAA treatment-naive and the data cannot be extrapolated to those with a history of failure to DAA-based regimens, especially NS5A inhibitors.[23]

This study also found that the majority of HCV patients undergoing treatment continue to need long-term monitoring after achieving SVR. To our knowledge, published real-world data on this topic is lacking. However, our results are consistent with published reports of controlled clinical trials; Noureddin and colleagues recently reported that evidence of significant steatosis (determined via transient elastography with controlled attenuation parameter) was found in 47.5% of 101 post-SVR patients and, of these, 6.25% had advanced fibrosis.[24] A larger study (n = 834) found that 35% of patients had ongoing hepatic inflammation, determined by elevated aminotransferase levels, despite HCV eradication.[25] Surveillance for hepatocellular carcinoma is recommended in these patients, per published guidelines, due to the presence of pretreatment advanced fibrosis and/or persistent ALT elevation after achieving SVR. This indicates the possibility of additional, underlying chronic liver disease (e.g., nonalcoholic fatty liver disease [NAFLD], alcoholic liver disease [ALD]) which can lead to further fibrosis progression and heightened risk of hepatocellular carcinoma.[9,10] Therefore, in most cases, patients should not be discharged from the care of a liver specialist solely because virologic cure was achieved.

As this was an observational study, only standard of care data were collected. On the subject of HCV treatment, the most recently approved DAA regimens were not included due to the fast pace of HCV drug development; however, newer DAA regimens are currently being assessed. As for resistance, baseline resistance testing was done in the majority of, but not all, patients and, although only 25% of our patient population received prior HCV treatment, ~60% had detectable RASs before DAA treatment. This rate is higher than that reported in the literature, albeit registration studies.

Regarding chronic liver disease, we did not assess for the presence of NAFLD and ALD at baseline or post-SVR. Furthermore, the last ALT value post-SVR was collected and used to define patients with elevated ALT; persistence of ALT elevations beyond the post-SVR visit was not captured. Finally, although the study took place at community-based centers, local providers use these clinics as referral centers that may have

Table 4

Factors associated with the need for long-term follow-up in patients who achieved SVR (logistic regression).

	Odds ratio	Lower 95% CI	Upper 95%CI	*P*
Pretreatment platelet count	0.96	0.90	0.99	<.001
Pretreatment creatinine	1.10	1.05	1.16	<.001
Pretreatment AST	1.12	1.06	1.20	<.001
Proposed 24-wk treatment duration (12-wk reference duration)	3.44	1.58	8.09	.003

AST = aspartate aminotransferase, CI = confidence interval, SVR = sustained virologic response.

contributed to the higher prevalence of advanced fibrosis in our cohort.

In conclusion, in a real-life, US cohort of HCV-infected patients, nearly all patients achieved SVR with available DAA regimens regardless of baseline RASs. However, approximately two-thirds of patients continue to need long-term follow-up due to advanced liver disease, despite viral eradication. These findings underscore the need for earlier HCV identification and treatment, modification of additional risk factors for chronic liver disease, and continued specialized care post-SVR.

Acknowledgments

The authors thank Martin W. Goros and Jonathan Gelfond for their assistance with the statistical analyses and Rachel Bejarano, PharmD, for writing assistance.

Research funded through Health Outcomes Centers.

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