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Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection

To the Editor:

Summary

Curative treatment of patients who previously failed hepatitis C virus (HCV) therapies is critical to achieving HCV elimination. Glecaprevir/pibrentasvir (G/P) demonstrated high rates of sustained virologic response at post-treatment week 12 (SVR12) in patients with HCV infection; however, retreatment of patients who failed G/P has yet to be evaluated.

MAGELLAN-3 is an ongoing, open-label, phase IIIb trial evaluating the efficacy and safety of G/P plus sofosbuvir (SOF) plus ribavirin (RBV) as a retreatment regimen for patients who had virologic failure with G/P in an AbbVie study. Patients with HCV genotype (GT) 1, 2, 4, 5 or 6 infection, without cirrhosis, and naïve to NS3/4A protease and NS5A inhibitors prior to virologic failure with G/P received 12 weeks of treatment; patients with GT3, and/or compensated cirrhosis, and/or experience with NS3/4A protease and NS5A inhibitors prior to virologic failure with G/P received 16 weeks of treatment. The primary efficacy endpoint was the SVR12 rate. Safety, tolerability, and presence of resistance-associated substitutions (RASs) were assessed.

To date, 23 patients enrolled: 30% (7/23), 9% (2/23), and 61% (14/23) of patients had GT1, 2, and 3 infections, respectively; 30% (7/23) of patients had compensated cirrhosis, and 91% (21/23) had baseline RASs in NS5A. The SVR12 rate was 96% (22/23); 1 patient with GT1a infection and compensated cirrhosis had virologic failure. One unrelated serious adverse event (AE) of symptomatic cholelithiasis occurred. There were no treatment discontinuations.

Retreatment of G/P virologic failures with G/P plus SOF plus RBV for 12 or 16 weeks was well-tolerated and highly efficacious, regardless of HCV genotype or baseline RASs.

Introduction

Direct-acting antivirals (DAA) have revolutionized treatment of hepatitis C virus (HCV) infection with increased cure rates and interferon-free treatment options. One remaining difficult-to-cure population is patients who had virologic failure with prior HCV treatment(s), particularly those containing NS5A inhibitors (NS5Ai), since presence of resistance-associated substitutions (RASs) can pose additional challenges to treatment.[1–5] Treatment options in this population are limited,[6–7] and retreatment of DAA-experienced patients remains an important step towards the WHO goal for HCV elimination.[8]

The HCV NS3/4A protease inhibitor (PI) glecaprevir and the NS5Ai pibrentasvir are a once-daily, fixed-dose combination therapy (G/P) for chronic HCV infection.[9] Both DAAs maintain activity against common amino acid substitutions in HCV genotype (GT) 1–6 that are known to confer resistance to currently approved inhibitors.[10,11] In clinical trials, treatment with G/P yielded ≥ 95% sustained virologic response at post-treatment week 12 (SVR12) across all HCV genotypes, including patients with DAA experience; virologic failure rates were 0–1%.[12–17]

Data on a retreatment regimen for patients who fail G/P are limited. To increase the success of retreatment, adding ribavirin (RBV) and a DAA with a non-overlapping mechanism of action to an existing DAA regimen may be beneficial.[18–23] MAGELLAN-3 is an ongoing study evaluating the safety and efficacy of G/P in combination with sofosbuvir (SOF), an approved nucleotide analogue NS5B polymerase inhibitor,[24] and RBV (G/P + SOF + RBV) as a 12- or 16-week retreatment regimen for patients who experienced virologic failure in a G/P clinical study, designated as the Parent Study.

Patients and methods

MAGELLAN-3 is an ongoing phase IIIb, open-label, non-randomized, multicentre study. The trial protocol was approved by the independent ethics committee or institutional review board for each trial centre. The trial was conducted in accordance with the Good Clinical Practice Guidelines and the ethical principles of the Declaration of Helsinki; all patients provided written informed consent.

The data cut for this manuscript was February 22, 2018. Adult patients with HCV GT1–6 infection who had virologic failure with G/P (300 mg/120 mg) in a Parent Study were eligible for screening. G/P treatment must have been completed or discontinued at least 1 month prior to screening.

The retreatment regimen was comprised of once-daily G/P (300/120 mg) plus SOF (400 mg) and twice-daily weight-based RBV. Patients without cirrhosis who had non-GT3 infection and were naïve to PI and/or NS5Ai prior to virologic failure with G/P received 12 weeks of treatment. Patients with GT3 infection, compensated cirrhosis, and/or prior NS5Ai and/or PI treatment prior to first treatment with G/P received 16 weeks of treatment.

The primary endpoint was the proportion of patients with SVR12 (HCV RNA <15 IU/ml at post-treatment week 12), assessed in the intention-to-treat (ITT) population, which included all patients who received at least 1 dose of study drugs. The secondary endpoints were the proportion of patients with on-treatment virologic failure and post-treatment relapse, excluding cases of reinfection. RASs in HCV NS3 and NS5A were identified by next generation sequencing from patient samples collected at baseline and, when applicable, at time of failure. Safety and tolerability were assessed.

Demographics, efficacy and safety analyses were performed on the ITT population. The percentage of patients who achieved SVR12 and the rate of virologic failure were summarized with a

Keywords: HCV; Retreatment; G/P; RAS; Resistance.

2-sided 95% CI, $p \leq 0.05$ considered significant, using the Wilson score method for binomial proportions.

For further details regarding the materials and methods used, please refer to the supplementary information.

Results

The average time between virologic failure with G/P in the Parent Study and retreatment with G/P + SOF + RBV was 10.4 (4.6–21.8) months. Table S1 shows baseline demographics of 23 enrolled patients; 91% had baseline RASs in NS5A.

Retreatment with G/P + SOF + RBV yielded an overall SVR12 of 96% (22/23; 95% CI 79.0–99.2) (Fig. 1). There were no on-treatment virologic failures. One patient with GT1a infection treated with 16-week G/P + SOF + RBV relapsed at post-treatment week 4; the patient had failed treatment with SOF plus ledipasvir prior to failing G/P. Baseline analyses failed to detect (2% detection threshold) NS3 RASs, but identified Q30K and Y93H linked RASs in NS5A; at the time of failure, A156V in NS3 was again detected (it was present at the time of failure in the Parent Study), and Q30K and Y93H in NS5A were still present (Table 1). The patient was adherent to treatment. Both patients with HCV GT2 infection achieved SVR12; neither had RASs at baseline other than the common NS5A M31 polymorphism, which does not confer resistance to pibrentasvir (Table 1). All 14 patients with GT3 infection achieved SVR12; notably, 7/14 (50%) had multiple NS5A RASs at baseline (Table 1).

The retreatment regimen of G/P + SOF + RBV was well-tolerated, with no treatment discontinuations (Table S2). One serious AE occurred and is discussed in the supplement. Clinically significant laboratory abnormalities were rare. There were no toxicity-associated RBV dose reductions.

Discussion

Due to the success of DAA therapies in treating HCV infection, retreatment data for those with virologic failure are scarce. This is the first report on a retreatment regimen specifically for patients who have had virologic failure following G/P treatment. Upon retreatment with G/P + SOF + RBV, 22/23 (96%) patients achieved SVR12, including 14/14 (100%) with HCV GT3 infection, demonstrating that patients who previously failed G/P treatment can be successfully retreated.

The MAGELLAN-3 study population was both complex and diverse, particularly regarding prior treatment history and RAS

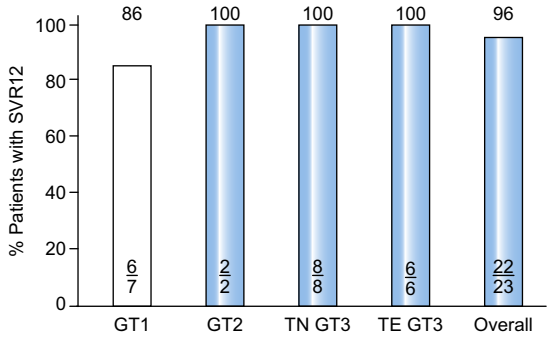

Fig. 1. Efficacy of G/P + SOF + RBV. Percentage of patients with sustained virologic response at post-treatment week 12 (SVR12), by genotype and overall, are shown; n/N inside bars.

profile. All HCV GT1-infected patients had virologic failure with at least 1 treatment prior to failing G/P treatment in the Parent Study; the majority (6/7) had failed a DAA-containing regimen prior to G/P treatment. This is in contrast to the GT3 population (61% of total patients), 57% of whom were treatment-naïve prior to receiving G/P treatment. While the study population was relatively small, it is noteworthy that 21/23 (91%) of patients had baseline NS5A RASs, and 14/23 (61%) patients had multiple baseline NS5A RASs, including 1 GT1b-infected patient with an NS5A P32 deletion, which confers high-level resistance (>1,000×) to all NS5Ai *in vitro*. Moreover, 14/23 (61%) patients had baseline RASs that confer greater than 50-fold resistance to pibrentasvir *in vitro*. Therefore, it is notable that all but 1 patient with baseline NS5A RASs (20/21; 95%) achieved SVR12. In a recent study, 83% of DAA-experienced patients retreated with SOF/VEL/VOX had a baseline RAS; similar to our findings in this study, RASs did not appear to impact virologic response.[25] A low number of patients with baseline NS3 RASs were enrolled; this is partly due to only 3 amino acid positions being used in the NS3 analysis, based on substitutions at positions that are known to confer resistance to commercially available NS3 PIs. Moreover, NS3 variants disappear over time from the bloodstream after removal of drug-selective pressure;[2] the low number of patients' baseline samples with NS3 RASs is therefore expected given the mean time between virologic failure in the Parent Study and baseline resistance testing of this study. Generally, patients in the current study who failed G/P appeared to have a more complex resistance profile than those failing other DAA regimens.[19,25–28]

The small number of patients enrolled may limit the broad applicability of these results; however, the low rate of virologic failure with G/P in registrational trials (1%) prohibited a large sample size. The small number of patients also did not allow for a side-by-side evaluation of another DAA regimen, or more importantly, treatment duration comparison (12 *vs.* 16 weeks) and/or RBV-free treatment. Regarding the single patient who relapsed after 16 weeks of treatment, a longer duration of treatment could be considered. However, the objective of this study was to maximize the chances of cure, rather than to identify an optimal retreatment regimen, in patients who failed G/P. Further studies are needed to evaluate whether treatment duration could be shortened for some subgroups, and/or whether RBV could be eliminated. Interestingly, recent real-world data in patients who failed previous DAA therapies (not inclusive of G/P) treated with G/P + SOF with or without RBV for 12 or 16 weeks showed that 100% (14/14) of patients who completed the study achieved SVR12.[29]

The results of MAGELLAN-3 informed European HCV treatment guidelines, which state that a triple combination of sofosbuvir with a PI and an NS5Ai may be well suited to retreatment of DAA-exposed patients.[7] Although these guidelines also recommend the triple combination of SOF/VEL/VOX[30] for retreatment of DAA failures, they cede that combining SOF with the fixed-dose G/P regimen is particularly attractive, since pibrentasvir has a higher barrier-to-resistance than all other approved NS5A inhibitors *in vitro*.[7,11] The American Association for the Study of Liver Disease only recommends SOF/VEL/VOX for patients who failed previous treatment with a PI in combination with an NS5Ai, based on the results of the POLARIS-1 study.[6,19] Retreatment of GT1 G/P failures with SOF/VEL/VOX was not evaluated in POLARIS-1, however recent limited data demonstrate that 5/5 HCV GT1 patients and 8/9 HCV GT3 patients

Table 1. Treatment and Resistance History of Patients.

Genotype/ Subtype	Cirrhosis	Treatment prior to G/P parent study	Type of VF in parent study	NS3 RASs at G/P failure in parent study*	NS5A RASs at G/P failure in parent study*	Time from failure in parent study to retreatment in Magellan-3 (months)	NS3 RASs at BL in MAGELLAN-3*	NS5A RASs at BL in MAGELLAN-3*
1b	No	DCV + ASV	Relapse	None	L28M + P32del	10.3	None	L28M + P32del
1a	No	OBV/PTV/r + DSV + RBV; pegIFN + RBV + DCV	OTVF	A156G + D168A	Q30R + L31M + H58D	7.5	A156G, D168A/T	Q30R + L31M + H58D
1a	No	TVR, DCV; pegIFN/ RBV	Relapse	A156V	Q30R + L31M + H58D	12.6	None	Q30R + L31M + H58D
1a§	Yes	SOF + LDV	OTVF	A156V	Q30K + Y93H	8.6	None	Q30K + Y93H
1a	Yes	SOF + SMV; SOF + LDV	Relapse	R155K + A156T	M28G + Q30R	6.7	R155K	M28G + Q30R
1a	Yes	OBV/PTV/r + DSV	OTVF	D168A	M28G + Q30R	14	None	M28G + Q30R
1a	Yes	pegIFN + RBV	Relapse	None	Q30R + Y93N	9	None	Q30R + Y93N
2a	No	SOF + RBV	Relapse	None	None	5.2	None	None
2a	No	IFN + RBV	Relapse	None	None	11.3	None	None
3a	No	Naïve	Relapse	None	Y93H	7.0	None	Y93H
3a	No	Naïve	Relapse	None	Y93H	4.6	None	Y93H
3a	No	Naïve	OTVF	Q168R	A30K + Y93H	11.7	Q168R	A30K + Y93H
3a	No	Naïve	Relapse	None	A30K + Y93H	6.0	None	A30K
3a	No	Naïve	Relapse	Q168L	A30K + Y93H	11.8	Q168L	A30K + Y93H
3b	No	Naïve	Relapse	None	(A30K + V31M) + Y93H†	13.2	None	A30K + V31M + Y93H
3a	Yes	Naïve	OTVF	A156G	A30K + Y93H	10.3	Q168R	A30K + Y93H
3a	Yes	Naïve	Relapse	Q168L	A30K + Y93H	11.4	None	A30K, Y93H
3a	No	IFN + RBV	Relapse	None	Y93H	7.0	None	Y93H
3a	No	IFN + RBV	Relapse	None	L31F + Y93H	18.9	None	Y93H
3a	No	IFN + RBV	Relapse	Q168R	A30K + Y93H	8.1	None	A30K
3a	No	IFN + RBV	Relapse	None	A30K + Y93H	6.2	None	A30K + Y93H
3a	No	IFN + RBV	OTVF	Q168L	A30K + Y93H	21.8	None	A30K
3a	Yes	IFN + RBV	OTVF	A156G	A30K + Y93H	14.0	None	A30K + Y93H

ASV, asunaprevir; BL, baseline; DCV, daclatasvir; DSV, dasabuvir; G/P, glecaprevir/pibrentasvir; LDV, ledipasvir; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; OTVF, on-treatment VF; RAS, resistance-associated substitution; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; VF, virologic failure.
'+'indicates that at least 1 of the substitutions was present at >90% prevalence and all others were present at >50% prevalence
*The detection threshold was 15%. NS3 resistance-associated substitution (RAS) positions included in analyses were: 155, 156 and 168. NS5A RAS positions included in analyses were: 24, 28, 30, 31, 32, 58, 92, and 93.
§Patient with virologic failure
†GT3b wild-type NS5A sequence has K30 and M31; in addition, Y93H was present.

who failed G/P were successfully retreated with SOF/VEL/VOX.[19,31]

This study provides the first data showing that patients who had virologic failure with G/P can be successfully retreated with G/P + SOF + RBV for 12 or 16 weeks. The combination regimen yielded a 96% cure rate in the most difficult-to-cure patient populations, including those with cirrhosis, GT3 infection, multiple prior DAA treatment experience- and presence of multiple NS5A RASs at baseline. The frequency and profile of AEs was consistent with an RBV-containing regimen, and the laboratory profile was consistent with that observed in G/P registrational trials. These results are an encouraging step on the path to HCV elimination, providing a treatment option for the increasingly small but important subpopulation of patients who fail highly effective DAA therapies such as G/P, and whose retreatment options are limited.

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Conflict of interest
AbbVie sponsored the study, contributed to its design, participated in the collection, analysis and interpretation of the data, and in the writing, reviewing, and approval of the manuscript. All authors had access to relevant data. D Wyles: Consultant: AbbVie, Gilead and Merck; Research funds: AbbVie, Gilead and Merck. O Weiland: Speaker/Consultant: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and MSD/Merck. F Weilert: Study investigator: AbbVie. J-F Dufour: Advisory committees: AbbVie, Bayer, Bristol-Myers Squibb, Genfit, Gilead Science, Intercept, Merck, and Novartis; Unrestricted research grant: Bayer. S Gordon: Consultant: AbbVie, CVS Caremark, Gilead, and Merck; Grant Support: AbbVie, Gilead, Intercept, and Merck. A Stoehr: Speaker: AbbVie, Gilead, Janssen, and MSD; Advisor: AbbVie and ViiV. A Brown: Advisor/speaker/Research grants: Abbvie, Bristol-Meyers Squibb, Janssen, Gilead, and MSD. S Mauss: Speaker: AbbVie, Gilead, Janssen and MSD; Advisor: AbbVie, Gilead and MSD. F Poordad: Grant/research support: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept Pharmaceuticals, Merck; Speaker: Abbvie, Bristol-Myers Squibb, Gilead, Intercept Pharmaceuticals, Merck, Salix; Consultant/advisor: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck. B Yao, Z Zhang, L Rodrigues Jr, FJ Mensa and T Pilot-Matias: employees of AbbVie and may hold stock or stock options.

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Data sharing statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (*e.g.*, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.01.031.

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Rabbit HEV in immunosuppressed patients with hepatitis E acquired in Switzerland

To the Editor:

Hepatitis E virus (HEV) infection is one of the most common causes of acute hepatitis and jaundice in the world.[1,2] HEV is a positive-strand RNA virus classified in the *Hepeviridae* family. Human pathogenic strains belong to species *Orthohepevirus A* which comprises 8 genotypes (gt) infecting a broad spectrum of animals as well as humans.[3,4] Human-restricted gt 1 and 2 are transmitted by the fecal-oral route and can cause large, primarily waterborne outbreaks in resource-limited settings.[5] HEV gt 3 and 4 infection is caused by zoonosis in high-income regions. Zoonotic transmission of HEV is believed to result from the consumption of raw or undercooked pork or game meat, with certain regional specialties such as figatellu in the South of France[6] or mortadella di fegato in the Ticino region of Switzerland[7] representing high-risk alimentary sources. Congruent HEV sequences identified in a Swiss patient with hepatitis E and a suspected food source recently led Wist *et al.* to propose a new gt 3 subtype, provisionally named 3s, as being present in Switzerland.[7–9]

We recently described 93 patients with PCR-proven acute hepatitis E acquired in Switzerland.[10] While most HEV isolates clustered phylogenetically to a distinct gt 3 subtype, the limited length of the genotyping target and the lack of (sub)genotypes from Switzerland recorded in GenBank precluded robust subtyping. Recently, 4 full-length gt 3s sequences were deposited in GenBank (accession numbers MF346772, MF346773, MG573193 and KY780957), allowing for more accurate subtyping. The gt 3s sequences share greater than 95% similarity but only 73 to 88% similarity when compared to other gt 3 subtypes. We have thus been able to reassess subtype assignment of the gt 3 isolates described in our previous report as well as of all other independent isolates for a total of 114 patients (according to protocol 478/15 approved by our ethics committee [CER-VD]), comprising 104 with acute and 10 with chronic hepatitis E, collected in Switzerland and diagnosed in our center over a 5.5-year period of time (November 2011 until April 2017).

Plasma samples from all 114 patients were subjected to HEV genotyping following amplification of open reading frame (ORF) 2/3 (191–195 base pair) and ORF2 (592 base pair) sequences, as described in Fraga *et al.*[10] Subtype assignment and phylogenetic analyses were performed using the HEVnet genotyping tool (https://www.rivm.nl/en/Topics/H/HEVNet) and confirmed by BLAST[11] within the Geneious software (Geneious 11.1.5, https://www.geneious.com) using a local database containing 360 non-recombinant full-length HEV sequences available in GenBank in August 2018, each being annotated with the subgenotype provided by HEVnet (support values ≥94%). All sequences from this study have been deposited in GenBank (accession numbers MK342954-MK343086).

Of 114 cases of hepatitis E acquired in Switzerland, genotyping information based on the ORF2/3 region could be obtained for 98 samples (87%) (Table 1). Sixty-two ORF2/3 positive PCR-samples were also subjected to the ORF2 genotyping assay. Positivity of genotyping PCR assays was associated with viral load (89,250 *vs.* 2,550 IU/ml for ORF2/3 and 456,750 *vs.* 34,500 IU/ml for ORF2; Mann-Whitney *U*, $p < 0.0001$).

HEV gt 3 was identified in 95 of 98 (96%) samples; the remaining 3 were of gt 4 (Table 1). Sixty-eight of the 95 gt 3 isolates could be assigned to a subtype, including 64 from patients with acute and 4 from patients with chronic infection. Fifty-two

Table 1. Distribution of HEV genotypes and subtypes in 114 independent samples subjected to ORF2/3- and/or ORF2-based genotyping.

HEV genotype	3						4	n.i.	Total
HEV subtype	3a	3f	3o*	3ra	3s*	n.a.			
Acute hepatitis E	2	6	4	1	51	22	3	15	104
Chronic hepatitis E		1		2	1	5		1	10
Total	2	7	4	3	52	27	3	16	114

n.a., non assigned to a subtype; n.i., non informative, i.e. the genotyping PCR was negative.
* Provisional subtype assignment according to HEVnet.