

Sofosbuvir/Velpatasvir/Voxilaprevir for Previously DAA-treated Patients with Chronic Hepatitis C?

Llaneras J^{1,2*}, Riveiro-Barciela M^{2,3}, Esteban R^{2,3}, Buti M^{2,3}

¹Emergency Room Department, Vall d'Hebron University Hospital, Barcelona, Department of Medicine of UAB (Universitat Autònoma de Barcelona), Spain

²Liver Unit, Internal Medicine Department, Vall d'Hebron University Hospital, Barcelona, Spain

³Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto Carlos III, Barcelona, Spain

*Correspondence should be addressed to Llaneras J; jllanera@vhebron.net

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Introduction

Chronic hepatitis C infection is a global public health problem affecting more than 71 million people. Treatment of hepatitis C virus (HCV) has rapidly advanced with the introduction of oral direct-acting antivirals (DAAs). Interferon-free DAA combinations have changed the treatment paradigm in HCV, with elimination of the infection in more than 95% of cases. Nonetheless, there remains a low rate of patients who fail these treatments and require a second-line rescue therapy. One of the latest additions to the HCV therapeutic armamentarium is the combination of sofosbuvir, velpatasvir, and voxilaprevir (SOF/VEL/VOX). The sofosbuvir 400 mg, velpatasvir 100 mg, and voxilaprevir 100 mg combination for 12 weeks has been recommended as rescue therapy for patients who experience chronic HCV recurrence following treatment with DAAs [1,2].

Clinical trials evaluating the efficacy and safety of sofosbuvir, velpatasvir, and voxilaprevir in previously treated patients

Open label phase II studies showed that SOF/VEL/VOX for 12 weeks is highly effective, yielding SVR12 rates greater than 96% in cirrhotic and non-cirrhotic HCV patients infected by any genotype and failing previous DAA treatments [3-6]. The pivotal phase III studies, POLARIS-1 and POLARIS-4, evaluated the efficacy of the SOF/VEL/VOX combination in patients who had failed previous DAA combinations with or without an NS5A inhibitor, regardless of the genotype or fibrosis stage, and

reported SVR12 rates higher than 96% [7,8]. Resistance-associated substitutions (RAS) were analyzed in both these studies, and RAS detected in more than 15% of sequences were reported. Despite detection of numerous RAS, these did not have an impact on SVR12, with high cure rates observed in both studies. As in the phase II studies, no relevant serious adverse effects were reported in POLARIS-1 and POLARIS-4. Headache, fatigue, diarrhea, and nausea were the most commonly documented side effects (in around 10% of patients) in all studies. Given the good tolerance, high adherence patterns could be ensured, allowing completion of the prescribed treatment.

Drug-drug interactions in sofosbuvir, velpatasvir, and voxilaprevir treatment

When starting treatment with SOF/VEL/VOX, it is mandatory to check whether interactions may arise with other medications prescribed for the patient [1,2]. SOF/VEL/VOX is a substrate of the P-glycoprotein transporter, and velpatasvir and voxilaprevir are substrates of the CYP450 system [9]. Hence, other drugs that are metabolized through these pathways can compete with SOF/VEL/VOX and decrease plasma levels of the combination. Gastric acid inhibitors should be used with caution because they may decrease velpatasvir concentrations. It is recommended to avoid taking proton pump inhibitors during SOF/VEL/VOX treatment, and if they cannot be suspended, there should be a minimum separation of 4 hours between administration of the drugs [9]. Concomitant use of amiodarone, anticonvulsants, cyclosporine, or rifampicin with SOF/VEL/VOX is contraindicated. Drugs such as

digoxin, dabigatran, or statins should be closely monitored because of a potential risk of toxicity [9]. Likewise, there are numerous interactions with retroviral therapy, mainly protease inhibitors, which advises caution when starting treatment in a patient with HIV coinfection [9].

Regarding safety of the rescue combination, the Food and Drug Administration (FDA) published an alarm notification after receiving notice of decompensated cirrhosis and acute liver failure in patients with advanced liver disease (Child-Pugh B or C) initiating treatment with SOF/VEL/VOX [10]. Therefore, use of this treatment is restricted and it is not indicated in patients with advanced liver disease and impaired liver function.

Real-world experience with sofosbuvir, velpatasvir, and voxilaprevir

Real-life studies on the effectiveness and safety of SOF/VEL/VOX as rescue treatment for HCV patients failing initial interferon-free DAA regimens are limited. In a recent study, we evaluated the real-life effectiveness of SOF/VEL/VOX in a multicenter cohort of 137 patients previously failing DAA treatment without interferon, including cirrhotic patients (34%), patients coinfecting with HIV (4%), and a representation of all HCV genotypes, with the majority being 1b (39%), 1a (22%), and 3 (22%) [11]. The previous therapy most often used was a combination based on sofosbuvir with an NS5A inhibitor in 62%, mainly ledipasvir (38%) and daclatasvir (18%). SOF/VEL/VOX treatment was well tolerated and there were no relevant adverse effects. The combination was highly effective, with an overall SVR12 rate of 95%, which was lower in cirrhotic patients (89%) and genotype 3 patients (80%). Seven patients failed: all had advanced fibrosis (4 were cirrhotic), 6 were genotype 3 patients, and 5 had received a combination of sofosbuvir plus daclatasvir. The results of this real-life study verify that the SOF/VEL/VOX combination is highly effective rescue therapy for patients failing first-line DAA treatments, achieving SVR12 rates higher than 95%, with a somewhat lower rate in genotype 3 patients and those with advanced fibrosis. The presence of RAS was determined in around half the patients included in the study. Although 87% of these patients had RAS conferring resistance to NS5A inhibitors, 25% to NS3 inhibitors, and 7% to NS5B inhibitors, the presence of these RAS did not have an impact on the sustained virologic response. In addition to those reported, currently 8 other patients in our setting have received SOF/VEL/VOX (September 2018-December 2019): 88% males, mean age 53 years, and 5 (63%) HIV coinfecting. Most were infected by HCV genotype 1b (38%) followed by 1a (25%). None had liver cirrhosis. Half had previously received a glecaprevir/pibrentasvir regimen. All patients achieved SVR12 and there were no adverse events. All these results

are consistent with the findings in the phase III POLARIS studies.

SOF/VEL/VOX rescue treatment has been investigated in several other real-life cohorts, and all have reported results indicating high effectiveness of the combination. In the United States, the largest real-life study was conducted in the Department of Veterans Affairs (VA) cohort by Belperio et al. [12]. The study included 573 patients and there was a broad representation of genotype 1 in relation to the other HCV genotypes (69% genotype 1a, 16 genotype 1b, 9% genotype 3, and 6% other genotypes). This distribution differed slightly from that of our study, as ours is a European cohort with a predominance of genotype 1b and a higher representation of genotype 3. In Belperio's study, 35% of the patients included had cirrhosis and 3% were coinfecting with HIV. The most widely used regimen patients had failed was the combination of an NS5A inhibitor and NS5B inhibitor. SOF/VEL/VOX rescue therapy was highly effective in the VA cohort, with SVR12 rates higher than 95% in genotype 1 and 93% in genotype 3, with no significant differences between cirrhotic and non-cirrhotic patients, or between genotypes. A previous history of hepatocarcinoma was the only factor with an impact on SVR12 in the genotype 1 group. Patients with genotype 1, 2, or 3 and prior SOF/VEL experience had lower SVR12 rates. None of the patients had received previous treatment with the sofosbuvir plus daclatasvir combination. Hence, the results of this study cannot corroborate our findings in which genotype 3 patients previously treated with sofosbuvir plus daclatasvir had lower response rates to SOF/VEL/VOX. An interesting aspect of the study by Belperio et al. is inclusion of patients with decompensated cirrhosis, who showed high sustained virologic response rates (>90%).

Another real-life study conducted in the United States through the TRIO Network included 173 DAA-experienced patients [13]. Among the total, 42% had cirrhosis, 60% were infected by genotype 1a, and 16% by genotype 3. Results similar to those of the VA cohort were obtained, with SVR12 rates higher than 94%.

The results of real-life studies in Europe also support the effectiveness and safety of SOF/VEL/VOX treatment. Vermehren et al. (German Hepatitis C Registry [DHC-R]) reported their experience with 74 patients who had failed DAAs [14]. Genotype 1 was predominant in 71% of cases, followed by genotype 3 in 34%. At the time of retreatment, 27% of patients had cirrhosis. Effectiveness was high, with 100% of patients achieving SVR12, and no serious adverse effects were documented, the most frequent being fatigue and headache. Another real-life study conducted in France included 46 patients who had previously failed DAAs [15]. The patients received SOF/VEL/VOX plus ribavirin for 8

weeks (n=10) or SOF/VEL/VOX without ribavirin for 12 weeks (n=36). All genotypes were represented, 90% were cirrhotic, and 11% were coinfecting with HIV. SVR12 rates higher than 95% were reported in the 44 patients who completed treatment.

The largest real-life study in Europe investigating the SOF/VEL/VOX combination as rescue treatment for DAA failures was performed in Italy by Degasperi et al. [16]. In total, 179 patients were included with an HCV genotype distribution similar to that of our study: Genotype 1b (33%), genotype 1a (24%), and genotype 3 (23%) predominated. In addition, 44% of patients had cirrhosis and 15% HIV coinfection. Most patients had failed the combination of sofosbuvir with an NS5A inhibitor. A baseline resistance study was available in 64% of patients, and some type of RAS was detected in 82% of those who underwent this study. Nonetheless, the presence of RAS did not significantly impact SVR12, in keeping with the findings in our study. The regimen was effective, yielding an overall SVR12 rate of 96%. Seven patients did not achieve SVR12. Of interest, all failures were cirrhotic patients, 3 were infected with genotype 3, and 2 of these 3 had previously received the sofosbuvir plus daclatasvir combination. Although the number of patients studied was relatively small, these findings support our observation that cirrhotic, genotype 3 HCV patients who previously failed the combination of sofosbuvir plus daclatasvir may have a poorer response to rescue SOF/VEL/VOX treatment.

SOF/VEL/VOX retreatment in difficult-to-treat populations

The SOF/VEL/VOX combination has shown high efficacy in various phase III and real-life studies. Some of these have included a small number of cases considered to be difficult-to-treat, such as patients with HIV coinfection or psychiatric disorders where adherence is lower, but there are no large studies evaluating SOF/VEL/VOX in these special populations. In the real-life studies cited above, including limited representations of coinfecting patients, HIV did not seem to have a major impact on SVR12, as HCV cure rates were similar to those of patients without coinfection. The Resolve Study, a multicenter open-label study carried out by Wilson et al., evaluated the tolerability, efficacy, and safety of SOF/VEL/VOX treatment in HCV patients with and without HIV coinfection [17]. Seventy-seven patients were included, all with HCV genotype 1 (75% 1a and 25% 1b); 17 patients (22%) were HIV coinfecting and 40% were cirrhotic. The most widely used previous treatment combinations were sofosbuvir/ledipasvir (89%) and sofosbuvir plus daclatasvir (5%). All patients with HIV infection were receiving retroviral treatment, mainly dolutegravir co-formulated with abacavir/lamivudine in 47%. Of note, 29% of patients reported poor compliance

with the previous DAA treatment, the main cause being poor adherence in 18%. SVR12 was higher than 90% overall and 82% (14/17) in the group with HIV coinfection, in which 1 patient had a virological relapse and 2 others abandoned treatment due to adverse effects. In general, the treatment was well tolerated: no significant differences in serious adverse effects were reported in the group with HIV coinfection relative to those without. The Resolve Study concluded that retreatment with SOF/VEL/VOX in HIV-coinfecting patients is effective even in patients with poor adherence to previous DAA treatment. The authors reported that the treatment was well tolerated, with no additional adverse effects in the HIV-coinfecting patients.

To date, there are no major real-life studies in difficult-to-treat populations. Given the good results in the small numbers available, it can be hypothesized that there are no factors in these patients to suggest a low response to SOF/VEL/VOX rescue treatment, although protocolled studies are required to prove this assumption.

Retreatment in patients who fail sofosbuvir, velpatasvir, and voxilaprevir

Although SOF/VEL/VOX treatment has shown high response rates in real-world studies, some patients fail this rescue therapy. Currently, there are no clear treatment indications for patients who fail the combination, and retreatment options are very limited. Based on real-life findings, it would be helpful to establish which patients may have a less successful response to SOF/VEL/VOX treatment. In our opinion, a potential example could be cirrhotic patients infected with genotype 3 who previously received treatment with sofosbuvir plus daclatasvir. Considering the results of the TRILOGY-3 study, we would contemplate adding ribavirin to the twelve-week SOF/VEL/VOX rescue regimen in these patients [6]. It should be noted that TRILOGY-3 reported that addition of ribavirin did not improve the study outcomes regarding SVR12, but a sub-analysis showed that effectiveness was maintained after adding ribavirin in patients with previous RAS. The American Association for the Study of Liver Disease (AASLD) guidelines recommend adding ribavirin in previously treated, genotype 3, and cirrhosis patients [2]. These same guidelines could be considered for rescue treatment in patients failing SOF/VEL/VOX, although this is a conjecture derived from clinical experience without supporting evidence from dedicated studies.

Conclusion

In conclusion, the small number of available real-world studies on HCV failures to DAAs indicate that rescue therapy with SOF/VEL/VOX is highly effective, achieving SVR12 rates higher than 90%. There is no clear evidence

Type of study	HCV genotype	Origin	Population	Cirrhosis	N	Duration	SVR12	Particularities
Phase II	Lawitz et al. [3]	USA, New Zealand	Cohort 2: DAA-experienced	Yes	63	12w	100%	Cohort 1 analyzed naive patients
	LEPTON [4]	New Zealand	DAA-experienced	Yes	68	8w	89%-100%	Treatment-experienced with PegIFN were included
	Gane et al. [5]	New Zealand	Cohort 2: DAA-experienced	Yes	65	12w	97%-100%	Cohort 1 analyzed naive patients
	TRILOGY [6]	USA	DAA-experienced	Yes	49	12w	96%-100%	25 patients received SOF/VEL/VOX plus ribavirin
	RESOLVE study [17]	USA	DAA-experienced	Yes	77	12w	91%	22% were HIV coinfecting patients without tolerance problems or DDI
Phase III	POLARIS-1 [7]	USA, Canada, New Zealand, Australia, France, Germany, and United Kingdom	DAA-experienced [without NS5A inhibitor]	Yes	263	12w	96%	High representation of genotype 1 [38% GT1a and 17% GT1b] and genotype 3 [30%]
	Substudy of POLARIS-1 [8]	GT 1 and GT 6	DAA-experienced [without NS5A inhibitor]	Yes	147	12w	97%	Cohort of patients receiving placebo in the POLARIS-1 study
Real-life	Belperio et al. [12]	USA [Department of Veterans Affairs]	DAA-experienced	Yes	573	12w	95%	Lower SVR12 rates in GT 1, 2 and 3 patients with prior SOF/VEL experience.
	Vermehren et al. [14]	Germany	DAA-experienced	Yes	74	12w	100%	Four patients had received SOF/VEL/VOX plus ribavirin previously.
	Degasperti et al. [16]	Italy	DAA-experienced	Yes	179	12w	96%	Cirrhosis and hepatocellular carcinoma were predictors of treatment failure

DAA: Direct Acting Antiviral; DDI: Drug-Drug Interaction; GT: Genotype; PegIFN: Pegylated-Interferon; SVR12: Sustained Virologic Response at 12 weeks; w: weeks

Table 1: Summarize of phase II, phase III and real-life trials of Sofosbuvir/Velpatasvir/Voxilaprevir.

that defines risk factors for a poor response, although genotype 3 patients with cirrhosis show a tendency to lower response rates. In our study, patients failing rescue therapy were genotype 3 cirrhotic patients, most of whom had received previous treatment with sofosbuvir plus daclatasvir. Given the small number of patients, causality cannot be attributed to this previous therapy and a bias based on previous guidelines cannot be ruled out. Nonetheless, we believe that these factors should be considered in future studies. RAS have been determined in patients failing DAA therapy in a few studies, and the results indicate that patients carrying RAS prior to initiation of rescue treatment do not have worse response rates. This finding should be taken with caution given the limited number of patients implicated. In the light of a possible future failure, it is currently recommended to carry out resistance studies prior to initiation of SOF/VEL/VOX. On the other hand, SOF/VEL/VOX seems to be safe and effective for rescue treatment in HCV/HIV coinfecting patients, as effectiveness remains high in this population and serious or limiting interactions with retroviral treatment have not been reported.

SOF/VEL/VOX treatment is likely one of the last therapeutic steps in achieving a complete arsenal for the eradication of HCV infection, being a highly effective, safe, and almost universally applicable treatment for all HCV-infected patients.

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