Acta Biomed 2018; Vol. 89, N. 3: 321-331 DOI: 10.23750/abm.v89i3.7718

Review

Sofosbuvir/Velpatasvir for the treatment of Hepatitis C Virus infection

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Summary. Hepatitis C Virus (HCV) infection is major health problem worldwide, with 150 million infected people according to recent epidemiologic estimations. The introduction of direct-acting antivirals made a revolutionary change in the management of HCV infected patients with surprisingly high rates of antiviral response, improved tolerability and reduced time of treatment. Sofosbuvir, in combination with different partner drugs, has been the molecule that led this incredible change. The last generation of SOF-based regimens, namely Sofosbuvir/Velpatasvir, represents a single tablet, once a day, pangenotypic and pan-fibrotic combination, demonstrated to be safe and effective in almost all type of HCV infected individuals. This review overviews the main clinical data of SOF/VEL registration trials, underlying the key features of this combination in terms of efficacy, safety and Patients Reported Outcomes obtained in more than 1800 HCV chronically infected subjects. (www.actabiomedica.it)

Key words: HCV, Sofosbuvir, Velpatasvir, Single tablet regimen, PI-free

Introduction

150 million people are infected worldwide by the Hepatitis C Virus (HCV), which is a single stranded RNA virus from the Flaviviridae family with 6 major genotypes (GTs) (1, 2). Progressive liver fibrosis is caused by chronic HCV infection, which can induce cirrhosis, hepatic decompensation, and hepatocellular carcinoma. It is estimated that the annual mortality rate of half a million people is due to liver disease associated with chronic HCV infection (3).

An estimated 35% of global HCV infections are caused by HCV GTs 2 and 3, which affect roughly 58 million people (4). Contrary to GT1, GTs 2 and 3 are diffused in low-income regions such as Latin America, Asia, sub-Saharan Africa and Eastern Europe. HCV GTs 2 and 3 were categorized together in treatment guidelines and were classified as easy to treat genotypes before the introduction of direct-acting antiviral agents (4). According to recent studies, HCV GT3 is linked to rapid disease progression and has lower rates of response to treatment compared to GT2, as particularly demonstrated in patients with cirrhosis and in patients who have not reacted to earlier treatment (5, 6).

Patients with decompensated cirrhosis caused by HCV chronic infection is set to rise in the next decade (3). Liver transplantation was the only treatment option available to these patients until recently.

An additional challenge for clinicians is the eradication treatment in the HCV/HIV co-infected population (7). In fact, HCV/HIV-coinfected patients suffer from higher rates of cirrhosis and liver decompensation disease than their mono-infected counterparts (8).

HCV treatment has recently undergone a transformation with the development of drugs that directly impede HCV replication. Effective combinations of direct-acting antiviral agents are currently available. Clinicians must consider the patient's treatment history, HCV GT and subtype, stage of fibrosis, and pat-

terns of antiviral resistance in specific cases in order to select a suitable regimen.

Regimens which include ribavirin (RBV) show a higher rate of side effects, mainly hematologic and RBV-free combinations would allow a better management of a wider range of patients, including those with a low tolerance to RBV. This would in turn minimize the necessity for pretreatment testing and monitoring during therapy, aspects that could be especially beneficial in low-income countries.

Sofobusvir (SOF) is a nucleotide analogue inhibitor of the HCV NS5B polymerase approved for HCV treatment in conjunction with other agents, which include NS5A inhibitors, NS3/4A protease inhibitors (PI), RBV, and peginterferon-RBV. Velpatasvir (VEL) (also formerly known as GS-5816, Gilead Sciences) with antiviral activity against HCV replicons in GTs 1 to 6, is a last generation, pan-genotypic HCV NS5A inhibitor.

The SOF/VEL is a single tablet, once a day regimen that combines two pan-genotypic, high potency and high genetic barrier antiviral molecules, providing >95% of SVR across all GTs with favourable safety and tolerability across a broad patient population even for decompensated cirrhotic subjects.

The SOF/VEL pill is PI, gluten, and lactose free and can be used without RBV to address unmet needs in the HCV treatment paradigm.

ASTRAL studies

An evaluation of efficacy and safety on the combination of sofosbuvir and velpatasvir was reported in different patient populations by a series of Phase III clinical trials entitled ASTRAL (ASTRAL-1, ASTRAL-2, ASTRAL-3, ASTRAL-4, and ASTRAL-5) (9-12) (Figure 1).

The ASTRAL studies demonstrated that SOF/VEL is highly effective across all GTs and different stages of liver damage, and can therefore be defined as a pan-genotipic and pan-fibrotic regimen. The following ASTRAL studies were focused on particular patient settings, providing information with regard to the efficacy and safety of SOF/VEL in subpopulations of HCV-positive subjects, which were considered as difficult to treat until now.

ASTRAL populations and study design

ASTRAL-1 included patients infected with HCV GTs 1 to 6 with different stages of liver damage up to compensated cirrhosis, with the exclusion of GT3 infected patients (9). In the current DAA therapy era, GT3 infection has been relatively difficult to treat compared to other GTs, especially in subjects with cirrhosis or prior HCV treatment failure; therefore, a dedicated clinical trial study was set-up for those infected with GT3.

Patients were enrolled at 81 sites in North America, Europe, and Hong Kong. The study was double-blinded and placebo-controlled. Patients were randomized 5:1, with the exclusion of 35 patients infected with GT5, who only underwent SOF/VEL therapy, which was attributed to the low number. A total of 624 patients received at least one dose of the drug (116 patients received a placebo), 121/624 had compensated cirrhosis and 201/624 had experienced treatment.

The results of ASTRAL-2 and ASTRAL-3 studies are reported in the same manuscript (10), focused on HCV GT2 and HCV GT3 infected populations respectively. As mentioned in the introduction section, these two GTs, previously considered as easy to treat in the IFN-era, showed lower SVR rates for DAA-based therapies (5, 6).

ASTRAL-2 and ASTRAL-3 studies shared identical inclusion/exclusion criteria, and about 20% of patients with compensated cirrhosis were enrolled. Patients who underwent previous treatment were also included (20%/total). Subjects with decompensated cirrhosis and those who interrupted previous therapy as a result of adverse events were excluded. Patients were randomized 1:1 in both of the studies, in order to receive different SOF/VEL-based regimens (12 weeks with or without RBV in ASTRAL-2, 12 weeks or 24 weeks without RBV in ASTRAL-3). ASTRAL-2, enrolled 266 patients to initiate treatment from 51 sites in the United States while in ASTRAL-3, 552 patients from centers in North America, Europe, and Australia initiated therapy.

ASTRAL-4 was dedicated to naïve and experienced HCV patients with decompensated cirrhosis (CHILD-Pugh-Turcotte class B) (11). The study enrolled patients who did not receive a liver transplanta-

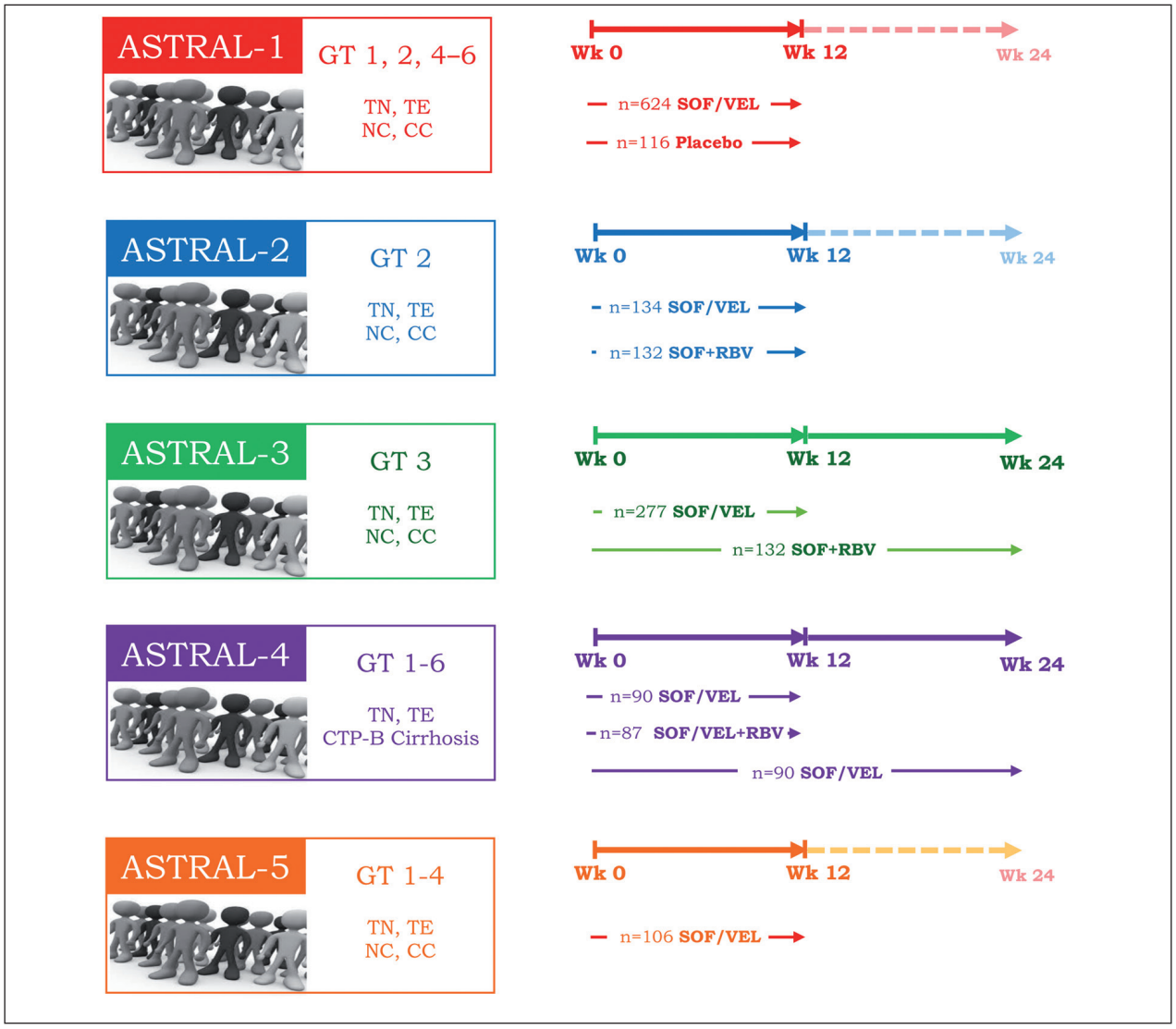

Figure 1. ASTRAL study design.
Legend: SOF: Sofosbuvir; VEL: Velpatasvir; RBV: Ribavirin; GT: genotype; TN: Treatment Naive; TE: Treatment Experienced; NC: Non Cirrhotic; CC: Compensated Cirrhosis; CTP-B Cirrhosis: Child-Turcotte-Pugh B Cirrhosis.

tion, or undergo antiviral treatment with any NS5A or NSB inhibitors, with a platelet count higher than 30,000/mm^3 and a creatinine clearance higher than 50 ml/min (Cockcroft-Gault equation). A total of 267 patients, recruited from 47 sites in the United States, initiated treatment with the following randomization: 90 patients received SOF/VEL for 12 weeks, 87 received SOF/VEL plus RBV for 12 weeks and 90 received SOF/VEL for 24 weeks. All of the HCV GTs except for GT 5 were represented.

Finally, to assess SOF/VEL efficacy and safety in HCV patients coinfected with HIV-1, ASTRAL-5, an open-label, single arm study, was performed (12). Patients were enrolled from 17 centers in the United States, and were required to be treated with an approved antiretroviral regimen, to acquire a HIV-1 viremia lower than 50 copies/mL and a CD4+ T-cell count higher than 100 cells/mL. Patients with compensated cirrhosis were also included, as well as experienced patients (excluding prior NS5A and NS5B inhibitors).

One hundred and six co-infected subjects initiated therapy consisting of a single pill of SOF/VEL once a day for 12 weeks (with the identical regimen and length for all the enrolled patients).

Efficacy across ASTRAL studies

The primary efficacy endpoint was common in all the ASTRAL studies, and was the rate of sustained virological response (SVR), defined as viremia lower than 15 IU/mL 12 weeks after therapy cessation in all the patients who received at least one dose of the drug after randomization. The secondary endpoints were different across the ASTRAL studies and depended on the specific enrolled populations and randomization.

ASTRAL-1 showed HCV infection and liver damage up to compensated cirrhosis in patients with GTs 1-6 (excluding GT3), and a SVR rate of 99% in patients who received SOF/VEL for 12 weeks, which is a significantly higher rate than the 85% value which was the pre-specified performance target. None of the subjects who received a placebo obtained an SVR (9).

The SVR rate was comparable among the different GTs (98% for GT1a, 99% for GT1b, 100% for GT2, 4, and 6, and 97% for GT5).

120/121 (99%) cirrhotic patients reached a SVR including 99.5% of experienced patients (9). Among non-cirrhotic patients 496/501 (99%) experienced a SVR (9).

ASTRAL-2 was a specifically required study by the Food and Drug Administration as a separated trial (10). The results showed a SVR rate of 99% in patients who received SOF/VEL for 12 weeks compared to 94% in those who underwent SOF plus RBV for 12 weeks. At the time the ASTRAL-2 study was performed, standard therapy showed a significant improvement in efficacy (10).

As reported in ASTRAL-3, HCV GT3 infected patients treated with SOF/VEL for 12 weeks reached a 95% SVR rate compared to 80% as shown by those receiving SOF plus RBV for 24 weeks, which is a highly significant difference in efficacy ($p<0.001$) (10). Considering non-cirrhotic GT3 patients, SOF/VEL led to SVR in 191/197 subjects (97%, while SOF plus RBV determined an SVR in 163/187 subjects (87%).

The SVR rate with all oral DAAs in decompensated cirrhosis was lower than in patients with less advanced liver disease (10).

The phase 3 ASTRAL-4 study aimed to evaluate the efficacy of SOF/VEL in the difficult-to-treat HCV-infected population, showing an eradication rate of 83% after 12 weeks of SOF/VEL, 94% after 12 weeks of SOF/VEL plus RBV, and 86% after 24 weeks of SOF/VEL (11). The SVR rate obtained from the different SOF/VEL based regimens did not show any significant differences. However, in decompensated cirrhosis caused by HCV GT3 infection, a SVR rate of 71% was previously reported (13) due to the fact that SOF/VEL plus RBV for 12 weeks resulted in 85% of the SVR.

The benefits of IFN-free therapy in advanced liver disease are still unclear. The secondary efficacy endpoints of ASTRAL-4 were linked to the improvement of liver damage, as the CPT and MELD scores changed at week 12 after therapy cessation (11). The analysis of CPT and MELD scores was performed on 250/267 patients; an improvement of CPT, compared to the baseline value, was observed in 47% of patients, and an improvement of MELD in 51% of those with a baseline value of less than 15, and in 81% of subjects with a MELD higher than 15. In general, such an improvement is due to a decrease in bilirubin levels and an increase in albumin levels (11). However, the long-term benefits on hepatic functions remain to be assessed.

Two efficacy endpoints were established in the ASTRAL-5 study, which was dedicated to the special population of HCV/HIV co-infected subjects (12). The first efficacy endpoint was common in the other ASTRAL studies and showed 95% of SVR in 106 HCV/HIV patients who underwent SOF/VEL for 12 weeks. All of the patients with cirrhosis reached a SVR (100%) along with 94% of the black patients and 94% of the experienced patients.

The secondary endpoint was the assessment of the percentage of real virological failures in patients who had viremia lower than 15 IU/mL during treatment. In fact, among the 5/106 patients not included in the SVR group, only 2 patients were virological failures (at week 4 of post-treatment), while 2 were lost during the follow-up, and 1 withdrew consent (12).

An integrated post-hoc analysis on antiviral efficacy considering the main Astral trials (Astral-1, -2 and -3) has been recently performed (14). The SOF/VEL treatment for 12 weeks in 1035 patients showed an overall SVR rate of 98% with an intention-to-treat analysis (Figure 2). The high efficacy was consistent across all genotypes, with only 2 virological relapse in GT1 and 11 in GT3 patients.

A retrospective analysis of efficacy results of SOF/VEL for 12 weeks for GT1–6 in phase 3 trials stratified by fibrosis stage has been recently proposed (15). The authors pooled patients data from SOF/VEL registration trials (ASTRAL-1 - NCT02201940, ASTRAL-2 NCT02220998, ASTRAL-3 NCT02201953) and SOF/VEL/VOX Polaris phase 3 studies (POLARIS-2 NCT02607800, and POLARIS-3 NCT02639338), where SOF/VEL treatment was considered as comparative arm.

Authors identified 1567 patients enrolled in the ASTRAL and POLARIS programs and a METAVIR category was assigned according to the FibroTest score (16). Demographics of the patient population stratified according to fibrosis score are summarized in Table 1 and Table 2.

The F0-F2 population was largely represented (n=887), with a mean age of 49 yrs, younger than F3 and F4 groups (57 and 58 yrs, respectively), as expected. GTs distribution was homogeneous between the groups with GT1 as the most prevalent except for the cirrhotic subjects where 37% of patients was infected by GT3. F4 group showed a higher proportion of experienced patients (40%) when compared to patients with milder fibrosis (20% and 28% for F0-2 and F3, respectively).

In addition to the Intention-to-treat (ITT) analysis, that considered all patients who were randomized and received ≥1 dose of assigned study drug, the Completer analysis was also performed, evaluating all patients who were randomized, completed assigned study treatment, and had HCV RNA data observed at post-treatment week 12 or imputed from a later timepoint.

SOF/VEL for 12 weeks was highly effective across all GTs regardless of degree of fibrosis as shown in Figure 3 and Figure 4 (15). Considering the Completer analysis, in the F0-F2 group almost all patients achieved an SVR (99.6%) with only 3 GT3 infected patients who relapsed out of 874 treated individuals (Figure 3). Similar high rates of response were registered also in patients with advanced fibrosis (F3: 232/234 SVR, 99.1%) and with cirrhosis (F4: 431/443 SVR, 97.2%) (Figure 4). In this latter group, high rates

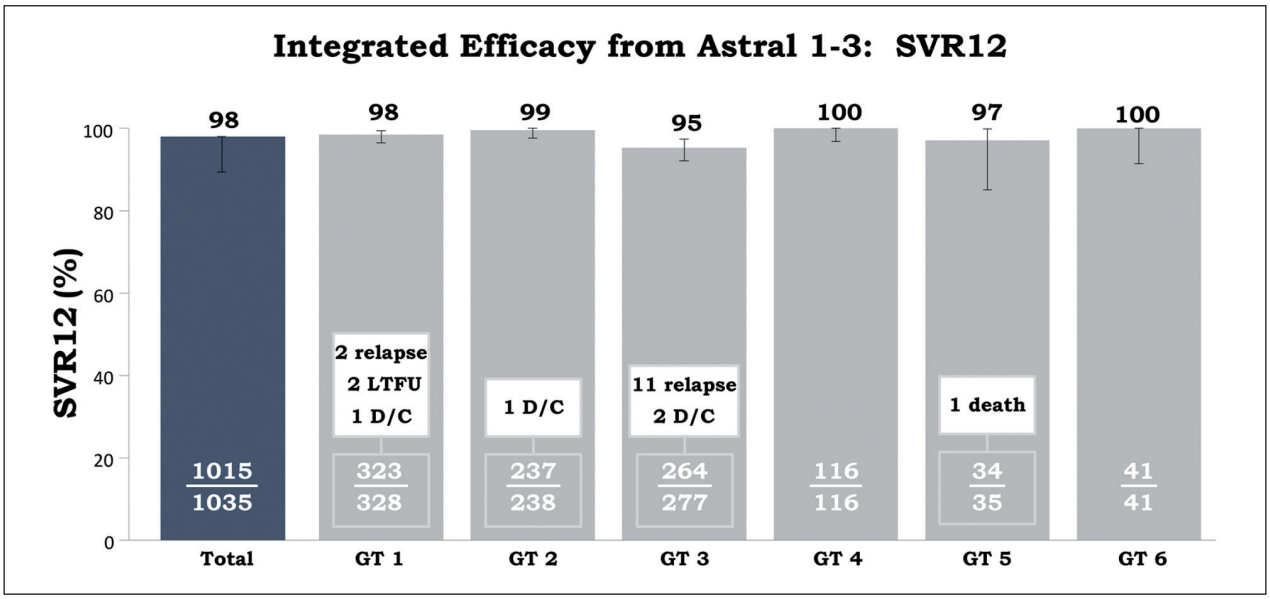

Figure 2. Integrated Intention To Treat Analysis of Efficacy from Astral 1-3: SVR12. SVR12: Sustained Virological Response 12; GT: Genotype; LTFU: Lost at Follow-Up; D/C: Discontinuation. Modified from (14).

Table 1. Demographic features of F0-F2 patients, treated for 12 weeks, from the Integrated analysis (ASTRAL and Polaris studies)

Total n of F0-F2 patients		887
Mean age, y (range)		49 (18-79)
Male, n (%)		421 (47)
Mean BMI, kg/m^2 (range)		26 (17-48)
HCV GT, n (%)	1a	205 (23)
	1b	102 (11)
	2	196 (22)
	3	227 (26)
	4	101 (11)
	5	24 (3)
	6	31 (3)
Baseline HCV RNA $\log_{10}$ IU/mL, mean (range)		6.3 (1.1-7.8)
Treatment Experienced, n (%)		177 (20)
F0, n (%)		337 (38)
F1, n (%)		160 (18)
F2, n (%)		390 (44)

Legend: BMI: Body Mass Index; GT: genotype; IU: International Units

Table 2. Demographic features of F3 and F4 patients, treated for 12 weeks, from the Integrated analysis (ASTRAL and Polaris studies)

		F3	F4
Total n of patients		236	444
Mean age, y (range)		57 (33-81)	58 (34-82)
Male, n (%)		162 (69)	355 (80)
Mean BMI, kg/m^2 (range)		28 (18-57)	28 (17-47)
HCV GT, n (%)	1a	67 (28)	107 (24)
	1b	26 (11)	48 (11)
	2	34 (14)	58 (37)
	3	77 (33)	164 (37)
	4	21 (9)	49 (11)
	5	5 (2)	5 (1)
	6	6 (3)	13 (3)
Baseline HCV RNA $\log_{10}$ IU/mL, mean (range)		6.3 (4.0-7.4)	6.2 (4.1-7.5)
Treatment Experienced, n (%)		66 (28)	176 (40)

Legend: BMI: Body Mass Index; GT: genotype; IU: International Units

of SVR were obtained also in GT3 patients (154/163, 94.4%) without the need for Ribavirin.

The ITT analysis showed minor differences, since only 16 patients out of 1567 were excluded from the Completer analysis (15).

Safety across ASTRAL studies

Rate of adverse events (AEs) and treatment discontinuation because of AEs was the secondary end point of the ASTRAL-1 study (9). Treatment was in-

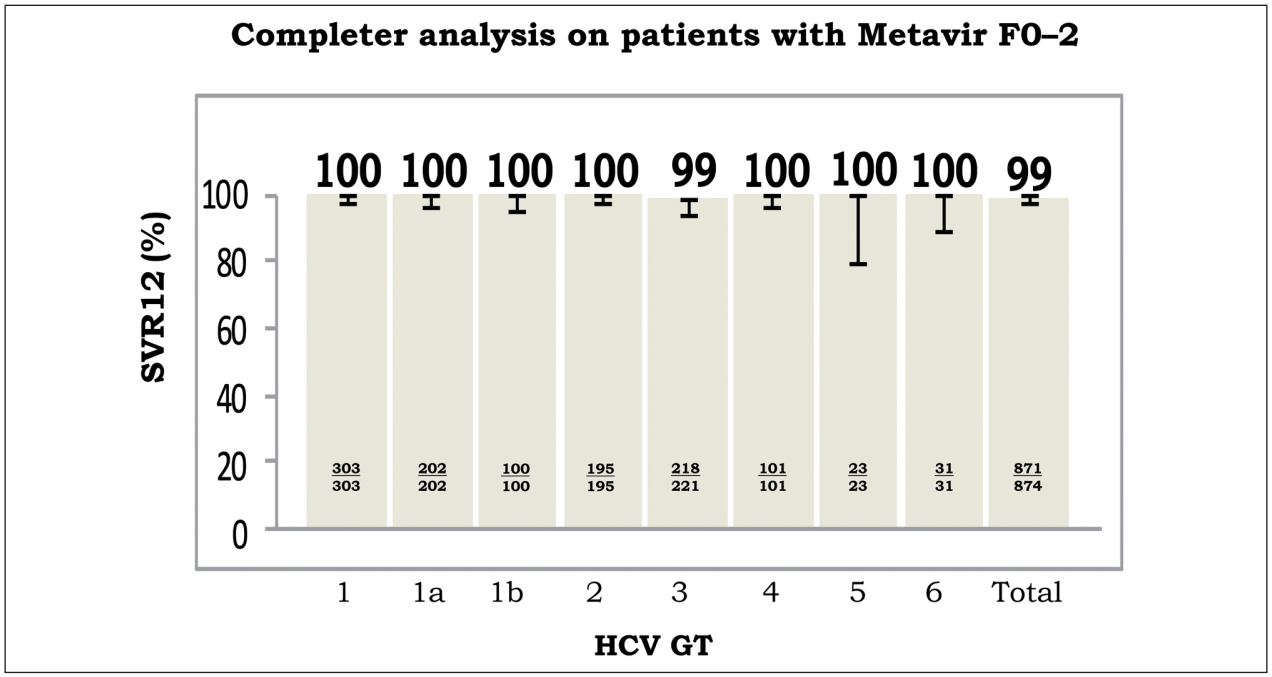

Figure 3. ASTRAL-1, -2, -3 and POLARIS-2, -3 combined retrospective analyses of efficacy in patients with METAVIR F0-F2, treated with Sofosbuvir/Velpatasvir for 12 weeks. Patients were treatment naïve and treatment experienced (including PI-failure); SVR: Sustained Virological Response; GT: Genotype. Modified from (15).

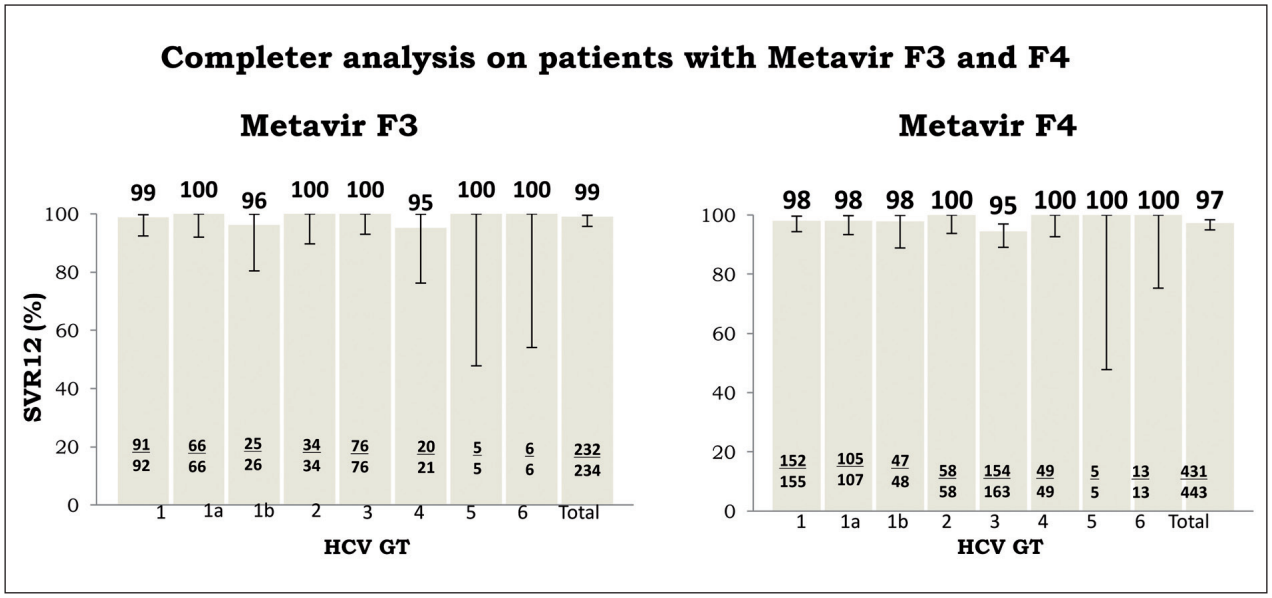

Figure 4. ASTRAL-1, -2, -3 and POLARIS-2, -3 combined retrospective analyses of efficacy in patients with METAVIR F3 and F4, treated with Sofosbuvir/Velpatasvir for 12 weeks. Patients were treatment naïve and treatment experienced (including PI-failure); SVR: Sustained Virological Response; GT: Genotype. Modified from (15).

terrupted by 1 patient (<1%) in the SOF/VEL group and by 2 patients (2%) in the placebo group. Serious AEs occurred in 15 patients (2%) treated with SOF/VEL and in none of the patients who received a placebo. Overall, AEs (mostly headache, nausea, fatigue and nasopharyngitis) were recorded in 78% of sub-

jects who underwent SOF/VEL therapy, and in 77% of those in the placebo group, without any significant difference (9).

In the ASTRAL-2 and ASTRAL-3 studies, a patient included in the ASTRAL-2 study interrupted treatment after the first pill due to anxiety and a headache (10). In ASTRAL-3, RBV was only discontinued by 9 patients (3%) as a result of AEs. In the ASTRAL-2 study, the percentage of serious AEs was the same in those who received and those who did not receive RBV (1%); in the ASTRAL-3 study, 2% of subjects who did not receive RBV experienced serious AEs compared to 15% of those who received RBV. Considering both studies, AEs were generally frequent in patients who underwent RBV-including regimens and the types of AEs were typical of RBV (anemia, insomnia, irritability and coughing). Two ASTRAL-2 patients died during the post-treatment follow-up and 3 ASTRAL-3 patients died during treatment. All the deaths seemed to be due to causes unrelated to therapy or were categorized as unknown (10).

As expected for the severe condition of the study population in terms of liver damage, the serious AEs rate was higher in the three groups of the ASTRAL-4 study with hepatic encephalopathy and sepsis being the most frequent and serious AEs (11). For the same reason, the nine deaths that occurred during the study were thought to be unrelated to treatment and were possibly ascribable to the end-stage of liver disease. Anemia was very common in 30% of patients who received RBV, and was experienced at a different level of severity.

ASTRAL-5 had a proportion of patients who interrupted treatment due to AEs as a primary safety end-point (12). In fact, 71% of patients experienced at least one AE, which was serious in only 2 cases (2%) and led to therapy discontinuation in one case. Another patient interrupted therapy as a consequence of a mild adverse event (a single vomiting episode) at day 48 and reached SVR12 regardless. None of the patients died and in none of the cases, the ARV was modified (12).

Pruritus was not observed in any patient of the ASTRAL studies among the AEs (9-12).

Overall, the SOF/VEL regimens demonstrated a very good safety profile in all the ASTRAL studies, which covered a wide range of the different features that are typical of HCV-chronically infected patients. Nevertheless, in the case of other concomitant treatments, caution is required in order to avoid drug-to-drug interactions (DDI) (17). SOF/VEL is not recommended for patients treated with amiodarone due to the risk of severe symptomatic bradycardia if taken together (17). Other drugs reduce SOF/VEL efficiency (antacids and proton pump inhibitors, some anticonvulsants, antimycobacterials, and chemotherapy topotecan) (17-19). However, the SOF/VEL regimen presents a very good DDI profile, which represents the best option in multi-treated patients with co-morbidities, in women of child-bearing potential, and in active drug users or in opioid substitution therapy (19-21). This makes SOF/VEL regimen suitable also for patients using recreational drugs, generally not mentioned during the anamnestic evaluation.

SOF/VEL can also be administered in patients with mild or moderate renal impairment, even if it is not recommended for patients with more severe renal damage (eGFR\30 mL/min/1.73 m^2).

The tolerability of SOF/VEL for 12 weeks was retrospectively assessed by an integrated safety analysis in more than 1000 patients treated in the ASTRAL-1, ASTRAL-2, and ASTRAL-3 studies (22). As showed by Table 3, SOF/VEL was well tolerated in HCV-infected patients with similar incidence and severity as in placebo treated subjects (Table 3). As reported in Table 4, the most common AEs emerging in SOF/VEL group from the integrated analysis were headache, fatigue, nausea, and nasopharyngitis, whose incidence was similar in placebo undergoing patients (Table 4).

Health-related quality of life and work productivity analysis in the ASTRAL studies

Patients with chronic HCV infection, usually have a poor health-related quality of life and impaired work productivity (23, 24). The patients reported outcomes are directly described by the patient and pertain to the patient's health, quality of life, or functional status associated with health care or treatment. The effect of SOF/VEL on PROs in HCV-patients included in the ASTRAL studies was performed (25, 26), and a

Table 3. Retrospective integrated analysis of data from 1,035 SOF/VEL for 12 Weeks patients and control/placebo patients in ASTRAL-1, -2, and -3

Patients, n (%)	SOF/VEL 12 weeks N=1035	Placebo 12 weeks N=116
AEs	821 (79)	89 (77)
Grade 3 or 4 AEs	33 (3)	1 (<1)
SAEs	23 (2)*	0
AE leading to treatment D/C	2 (<1)^	2(2)
Death	3 (<2)**	0)

Legend: SOF: Sofosbuvir; VEL: Velpatasvir; AEs: Adverse Events; SAEs: Severe Adverse Events; D/C: Discontinuation; *No SAE was assessed as related to SOF/VEL; **None were assessed as related to study treatment; ^Two subjects D/C SOF/VEL for AEs; (1 D/C day 1 due to difficulty concentrating, headache, and anxiety and 1 D/C day 13 of due to anxiety)

Table 4. More frequent adverse events from the retrospective integrated safety analysis of data from 1,035 SOF/VEL for 12 Weeks patients and control/placebo patients in ASTRAL-1, -2, and -3

Patients, n (%)	SOF/VEL 12 weeks N=1035	Placebo 12 weeks N=116
Headache	296 (29)	33 (28)
Fatigue	217 (21)	23 (20)
Nausea	135 (13)	13 (11)
Insomnia	87 (8)	11 (9)
Nasopharyngitis	121 (12)	12 (10)
Cough	57 (6)	4 (3)
Irritability	49 (5)	4 (3)
Pruritus	33 (3)	5 (4)
Dyspepsia	33 (2)	4 (3)

Legend: SOF: Sofosbuvir; VEL: Velpatasvir; severe adverse events were rare in SOF/VEL-treated patients, with headache, anxiety, and acute myocardial infarction occurring >1 patient (both cases of acute myocardial infarction were assessed as not related to SOF/VEL treatment by the investigators)

comparative analysis between patients with and without cirrhosis was also conducted (27, 28).

The analysis performed on the ASTRAL-1 patient groups showed that patients treated with SOF/VEL experienced a significant improvement in PROs during treatment and after SVR. In the placebo group, only one PRO improved by week 4 of treatment, and no further improvements were noted (25).

ASTRAL-2 and ASTRAL-3 populations were analyzed with regard to PROs in a dedicated study with a total of 818 HCV patients (25, 26). As previously mentioned, the overall rates of all adverse events were lower in the RBV-free SOF/VEL group (all $p<0.03$) and, therefore, patients who received RBV-free SOF/VEL regimens, reported significantly higher PRO scores during treatment compared to those who received the RBV-containing regimen (SOF plus RBV) (25, 26). At post-treatment week 12, changes from baseline levels were no longer different between the two treatment arms (25, 26).

Finally, a comparative analysis of PROs during and after SOF/VEL treatment in HCV patients with and without cirrhosis, from ASTRAL studies (1 to 4) was performed by Younossi and co-workers (27, 28). As expected, baseline PROs were lower in patients with cirrhosis, but, during SOF/VEL treatment and after reaching the SVR, subjects with and without cirrhosis experienced a significant improvement in the scores (27, 28).

In general, the administration of SOF/VEL produced a significant improvement in patients' quality of life, resulting in a benefit for the patients going beyond the SVR, as demonstrated by the PROs analysis of patients' perception of the treatment (25-28).

Conclusions

Data from phase III clinical trials on Sofosbuvir/Velpatasvir demonstrated that this antiviral combination addresses many unmet medical challenges. SOF/VEL make HCV treatment easier as the same therapy schedule are suitable for all the genotypes, irrespective of the fibrosis stage, making SOF/VEL a pan-genotypic and pan-fibrotic regimen. The presence of SOF warrantees high efficacy and minimal DDI and the combination with VEL, a last generation NS5A inhibitor, makes this regimen the standard of care for the treatment of chronic HCV infection.

The single-pill, once-a-day posology improves the adherence to the therapy and the absence of lactose and gluten make it suitable to patients intolerant or allergic to these substances.

SOF/VEL is a RBV-free regimen and in naïve non-cirrhotic patients attains SVR rates up to 100% in all genotypes. In decompensated cirrhotic patients, SOF/VEL, with the addition of RBV, resulted in 94% of SVR.

Actually, SOF/VEL is safe and effective on all-stages of liver disease, including decompensated cirrhosis, thanks to the absence of protease inhibitors

As a pangenotypic and pan-fibrosis regimen, it is conceivable that SOF/VEL will simplify, or perhaps eliminate, the pre-treatment assessments and on treatment monitoring that represent a barrier to treatment access in several countries. Considering the characteristics of SOF/VEL, this regimen can be considered the ideal partner in the path to HCV eradication.

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Received: 13 January 2018
Accepted: 23 April 2018
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