Efficacy and Safety of Sofosbuvir-Based Direct-Acting Antiviral Therapies for Hepatitis C Virus in Patients Receiving Opioid Substitution Therapy: An Analysis of Phase 3 Studies

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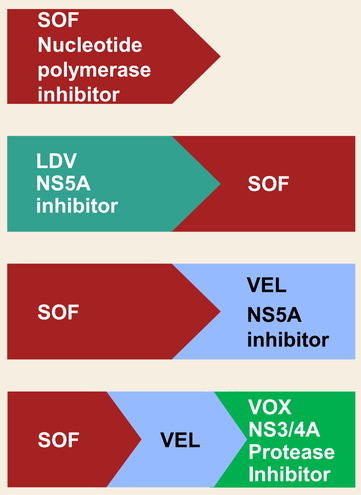
Introduction

- Sofosbuvir (SOF)
  - Once-daily, oral, 400-mg tablet used in combination with other medications
  - Potent antiviral activity against HCV genotypes (GT) 1–6
- Ledipasvir (LDV)/Sofosbuvir (SOF)
  - Once-daily, oral, fixed-dose combination (FDC, 90/400 mg) tablet
  - Single-tablet regimen (STR) for HCV GT 1, 4, 5, 6
- Sofosbuvir/Velpatasvir (VEL) FDC
  - Once-daily, oral, FDC (400/100 mg) tablet
  - Pan-genotypic STR for HCV GT 1-6
- Sofosbuvir/Velpatasvir/Voxilaprevir (VOX)
  - Once-daily, oral, FDC (400/100/100 mg) tablet
  - Pan-genotypic STR for HCV GT 1-6



Background

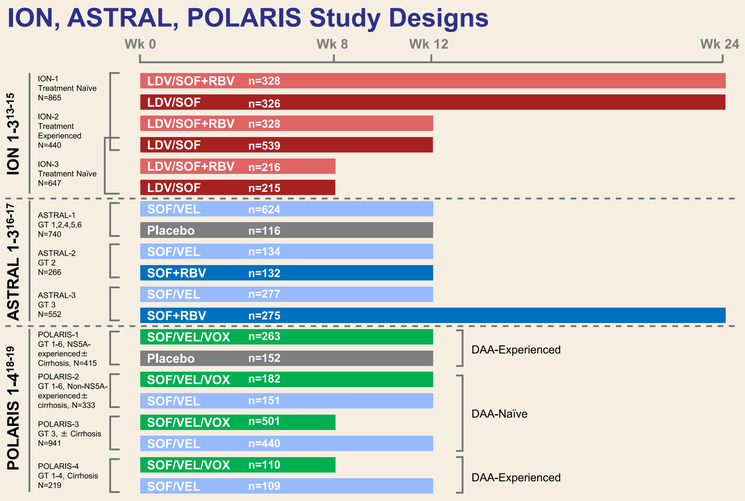
- People who inject drugs (PWID) are disproportionately affected by hepatitis C virus (HCV) infection[1-2]
- International guidelines recommend that all people should receive HCV treatment and that PWID should be prioritized, given the potential to reduce transmission to others[3-6]
- Interferon-based therapy is effective in people with a history of injecting drug use including those with recent injecting drug use and those receiving OST, with responses similar to that observed in large clinical trials[7-8]
- Although data are emerging on outcomes to DAA-based HCV therapy among PWID receiving OST, most studies are limited by small numbers of HCV non-genotype 1 patients[9-12]

Objective

- Evaluate the impact of OST on treatment completion, adherence, sustained virologic response 12 weeks post-end of treatment (SVR12) and safety of sofosbuvir-based therapy in patients receiving OST and not receiving OST in Phase 3 trials of sofosbuvir-based therapy

Methods

ION, ASTRAL, POLARIS Study Designs



RBV, ribavirin

Study Population

- Phase 3 trials: ION-1, -2 and -3; ASTRAL-1, -2 and -3; and POLARIS-1, -2, -3 and -4
  - Participants receiving OST (e.g. methadone or buprenorphine) were eligible for inclusion
  - Patients were excluded from enrolment in these studies if they had clinically significant drug use within 12 months of screening (as assessed by the investigator) or illicit drug use (excluding non-cannabinoids) detected by a positive urine drug test during the screening phase that was not explained by a prescription medication

Study Methods

- Post-hoc analysis of Phase 3 trials
- Endpoints included treatment completion, adherence, SVR12, safety, and reinfection
- Adherence was measured by counting the number of unused tablets in the returned bottles to derive the number of administrated tablets. In situations where a bottle was not returned, the number of tablets administered from that bottle was assumed to be 0
- SVR12 was defined as the absence of quantifiable HCV RNA in serum (<25 IU/mL or <15 IU/ml L) measured by COBAS® TaqMan® HCV Test, v2.0 (Roche Molecular Systems) at 12 weeks after the end of study treatment
- Participants were monitored for recurrence (viral relapse or reinfection) at 4 weeks, 12 weeks (SVR12), and 24 weeks (SVR24) following the completion of treatment
- Phylogenetic analyses were used to distinguish viral relapse from reinfection

Results

Baseline Demographics

	OST at enrollment (N=194)	No OST at enrollment (N=4549)
Mean Age (SD)	48 (10.7)	54 (10.4)
Male Sex, n (%)	141 (73)	2770 (61)
HCV Genotype, n (%)		
1a	84 (43)	2109 (46)
1b	12 (6)	816 (18)
2	14 (7)	409 (9)
3	74 (38)	787 (17)
4	10 (5)	269 (6)
5	0	54 (1)
6	0	86 (2)
Mean (SD) HCV RNA $\log_{10}$ IU/mL	6.3 (0.7)	6.3 (0.7)
HCV RNA ≥800,000 IU/mL, n (%)	142 (73)	3456 (76)
Cirrhosis, n (%)	70 (36)	1041 (23)
Treatment-experienced, n (%)	42 (22)	1568 (35)
Therapy		
Ledipasvir/sofosbuvir + ribavirin (8 weeks)	8 (4)	423 (9)
Ledipasvir/sofosbuvir + ribavirin (12 weeks)	32 (17)	835 (18)
Ledipasvir/sofosbuvir + ribavirin (24 weeks)	13 (7)	641 (14)
Sofosbuvir/velpatasvir (12 weeks)	92 (47)	1643 (36)
Sofosbuvir/velpatasvir/voxilaprevir (8 weeks)	41 (21)	570 (13)
Sofosbuvir/velpatasvir/voxilaprevir (12 weeks)	8 (4)	437 (10)
OST at Enrollment, n (%)		
Methadone	113 (58)	-
Buprenorphine	35 (18)	-
Buprenorphine/Naloxone	40 (21)	
Other	6 (3)	-

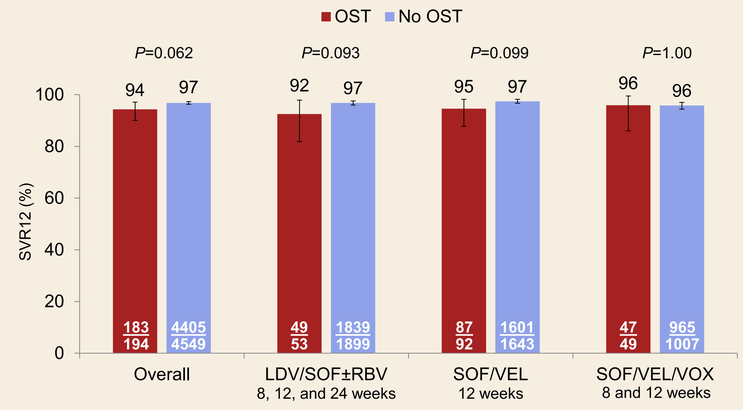
*19 patients were classified as other, unknown, or missing and all were not receiving OST at enrolment
Abbreviations: HCV, hepatitis C virus; OST, opioid substitution therapy; SD, standard deviation

Treatment Completion Rates

Characteristic	OST at enrollment	No OST at enrollment	*P*
Overall, % (n/N)[a]	189/194 (97.4)	4501/4549 (98.9)	0.064
Ledipasvir/sofosbuvir + ribavirin, % (n/N)	51/53 (96.2)	1863/1899 (98.1)	0.28
Sofosbuvir/velpatasvir, % (n/N)	89/92 (96.7)	1634/1643 (99.5)	0.022
Sofosbuvir/velpatasvir/ voxilaprevir, % (n/N)	49/49 (100.0)	1004/1007 (99.7)	1.00

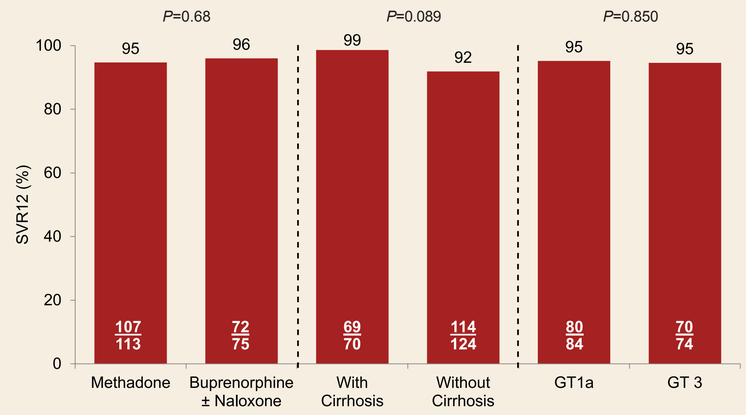
[a]The reasons for treatment discontinuation among patients receiving OST (n=5) included AEs (n=1); lost to follow-up (n=1); consent withdrawal (n=1); lack of efficacy (n=1); and non-compliance (n=1). The reasons for treatment discontinuation among patients not receiving OST (n=48) included AEs (n=19); lost to follow-up (n=10); consent withdrawal (n=6); protocol violation (n=6); lack of efficacy (n=4); non-compliance (n=1); and pregnancy (n=2).

SVR12: Overall and by Treatment Regimen (Intention-to-Treat Analysis)



- Overall, and by regimen, there was no difference in SVR12 between those who were and were not receiving OST therapy

SVR12 in OST Group:* by OST Type, Cirrhosis Status and GT 3 vs. GT 1a (Intention-to-Treat Analysis)



*Pooled data across treatment regimens and durations

- Patients receiving OST therapy achieved high SVR12 regardless of type of OST, cirrhosis status or if the patient had GT1a or GT3

Adverse Events

Characteristic	OST at enrollment	No OST at enrollment	*P*
Overall, % (n/N)			
Adverse events	152/194 (78.4)	3517/4549 (77.3)	0.79
Severe adverse events	7/194 (3.6)	108/4549 (2.4)	0.24
Ledipasvir/sofosbuvir + ribavirin			
Adverse events	47/53 (88.7)	1513/1899 (79.7)	0.12
Severe adverse events	2/53 (3.8)	50/1899 (2.6)	0.65
Sofosbuvir/velpatasvir			
Adverse events	68/92 (73.9)	1251/1643 (76.1)	0.62
Severe adverse events	4/92 (4.3)	33/1643 (2.0)	0.13
Sofosbuvir/velpatasvir/voxilaprevir			
Adverse events	37/49 (75.5)	753/1007 (74.8)	1.00
Severe adverse events	1/49 (2.0)	25/1007 (2.5)	1.00

Adverse event, n (%)	OST at enrollment			No OST at enrollment		
	Ledipasvir/ sofosbuvir + ribavirin (n=53)	Sofosbuvir/ velpatasvir (n=92)	Sofosbuvir/ velpatasvir/ voxilaprevir (n=49)	Ledipasvir/ sofosbuvir + ribavirin (n=1899)	Sofosbuvir/ velpatasvir (n=1643)	Sofosbuvir/ velpatasvir/ voxilaprevir (n=1007)
Adverse events in >10%						
Headache	12 (22.6)	20 (21.7)	8 (16.3)	443 (23.3)	450 (27.4)	269 (26.7)
Fatigue	19 (35.8)	18 (19.6)	11 (22.4)	556 (29.3)	364 (22.2)	222 (22.0)
Nausea	12 (22.6)	14 (15.2)	12 (24.5)	253 (13.3)	184 (11.2)	150 (14.9)
Diarrhea	4 (7.5)	7 (7.6)	5 (10.2)	151 (8.0)	110 (6.7)	183 (18.2)
Insomnia	5 (9.4)	5 (5.4)	3 (6.1)	232 (12.2)	112 (6.8)	59 (5.9)
Vomiting	4 (7.5)	6 (6.5)	6 (12.2)	60 (3.2)	42 (2.6)	24 (2.4)

Reinfection

- Two subjects were found to have reinfection with a different genotype than at baseline. Neither subject was receiving OST at baseline.
- One patient enrolled in ASTRAL-3 had genotype 3a at baseline and received SOF/VEL for 12 weeks. The patient achieved SVR4 and was found to have genotype 1a 12 weeks after the completion of therapy
- Another patient enrolled in POLARIS-2 had genotype 1a and received SOF/VEL for 12 weeks. The patient achieved SVR12, but was found to have genotype 3a 24 weeks after therapy

Conclusions

- This post hoc analysis of sofosbuvir-based therapies from the ION, ASTRAL, and POLARIS studies demonstrated high SVR12 rates among patients receiving OST, including those with HCV genotype 3 receiving sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir
- Similar treatment completion, SVR12, and AE rates were observed among patients with chronic HCV genotypes 1-6 receiving and not receiving OST
- Collectively, these data add to the body of evidence supporting the efficacy and safety of DAA treatment for HCV among people receiving stable OST, consistent with international recommendations[8-11]

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