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Efficacy and Safety of Simeprevir-Containing Hepatitis C Therapy in Patients on Opiate Substitution Therapy

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RATIONALE

HCV infection prevalence is high in patients with a history of intravenous drug use (IVDU) including those on opiate substitution therapy (OST)[1]. Simeprevir (SMV) is a HCV NS3/4A protease inhibitor approved in combination with pegylated interferon/ribavirin (PR) or sofosbuvir (±R) for the treatment of genotypes 1 and 4 HCV chronic infection. SMV has no drug-drug interaction (DDI) with methadone and no expected DDI with buprenorphine[2].

OBJECTIVE: To investigate whether the efficacy, safety and concomitant medication (CM) needs differ in SMV-treated patients on OST compared to SMV-treated patients not on OST (NOST).

METHODS

- Post-hoc analysis of pooled data across 11 SMV phase 2/3 prospective interventional studies and 1 US observational study.
- All patients (N=2439) were treated with SMV (150 mg QD) for a planned duration of at least 8 weeks (in combination with either PR or other DAAs±R).
- OST group: patients on buprenorphine±naloxone, methadone or morphine at start of treatment phase with an OST indication (n=44); patients who were prescribed these drugs for an unspecified indication (n=34) or chronic pain (n=4) were also included, provided they had been infected through IVDU or intranasal heroin use.
- NOST group: patients not receiving any opioid used for OST during treatment phase.
- SMV phase: first 12 weeks post baseline.
- DDI potential categories: CM were categorized as green, amber or red drugs based on information available at www.hep-druginteractions.org .
- Confidence intervals were estimated based on normal approximation to the binomial distribution. P-values were calculated using Chi-square test.

RESULTS

BASELINE CHARACTERISTICS

Parameter	OST N=83	NOST N=2356
Age, mean (SD), y	48 (12)	51 (11)
Male	61 (73)	1476 (63)
Race		
White	75 (90)	1957 (83)
Black/AA	7 (8)	302 (13)
Other/unknown	1 (1)	97 (4)
BMI, mean (SD), kg/m²	26 (5)	27 (5)
HCV GT		
1a	62 (75)	1151 (49)
1b	13 (16)	1013 (43)
1, other subtype/ unspecified	0	5 (<1)
4	8 (10)	166 (7)
Indeterminant /other	0	17 (1)
HCV RNA level, mean (SD), log_{10} IU/mL	6.3 (0.9)	6.4 (0.7)
Cirrhosis	21/82 (26)	484/2331 (21)
HCV treatment		
SMV+PR	46 (55)	1544 (66)
SMV+DAA±R	37# (45)	812 (34)
Treatment status		
Naive	58 (70)	1369 (58)
Experienced¥	25 (30)	987 (42)
OST*		
Buprenorphine	29 (35)	0
Methadone	43 (52)	0
Morphine	12 (14)	0

Results shown as n (%) unless otherwise indicated. AA: African American ¥DAA naïve *One subject took both buprenorphine and methadone
#49% (18/37) from US observational study (SONET)

CONCOMITANT MEDICAL CONDITIONS

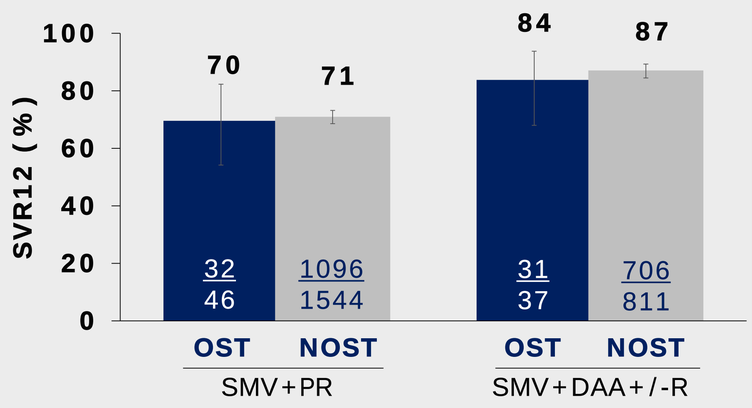
Prevalence ≥10%, n (%)	OST N=83	NOST N=2356
Depression	17 (20)	317 (13)
Hypertension	12 (14)	580 (25)
Anxiety	12 (14)	214 (9)
Diabetes	9 (11)	225 (10)

SUBSTANCE USE

n (%)	OST	NOST
	N=83	N=2356
Alcohol#	38 (46)	779 (33)
Tobacco#	50 (60)	624 (26)
	N=63	N=2040
Amphetamine+	2 (3)	8 (<1)
Cocaine+	3 (5)	11 (<1)
Opiates+	19 (30)	85 (4)
	N=48	N=1647
Barbiturate+	1 (2)	9 (<1)
	N=35	N=816
Benzodiazepines+	5 (14)	34 (4)
Cannabinoids+	11 (31)	93 (11)

From CRF screening Substance Use + From screening urinalysis; urine drug screening was not performed in studies HPC2010 (IMPACT) and HPC4003 (SONET). Not all substances were tested in all trials.

EFFICACY (ITT)



94% of patients had a ≥97% compliance rate to SMV (OST: 78/83, NOST: 2222/2356).

SAFETY (during SMV phase)

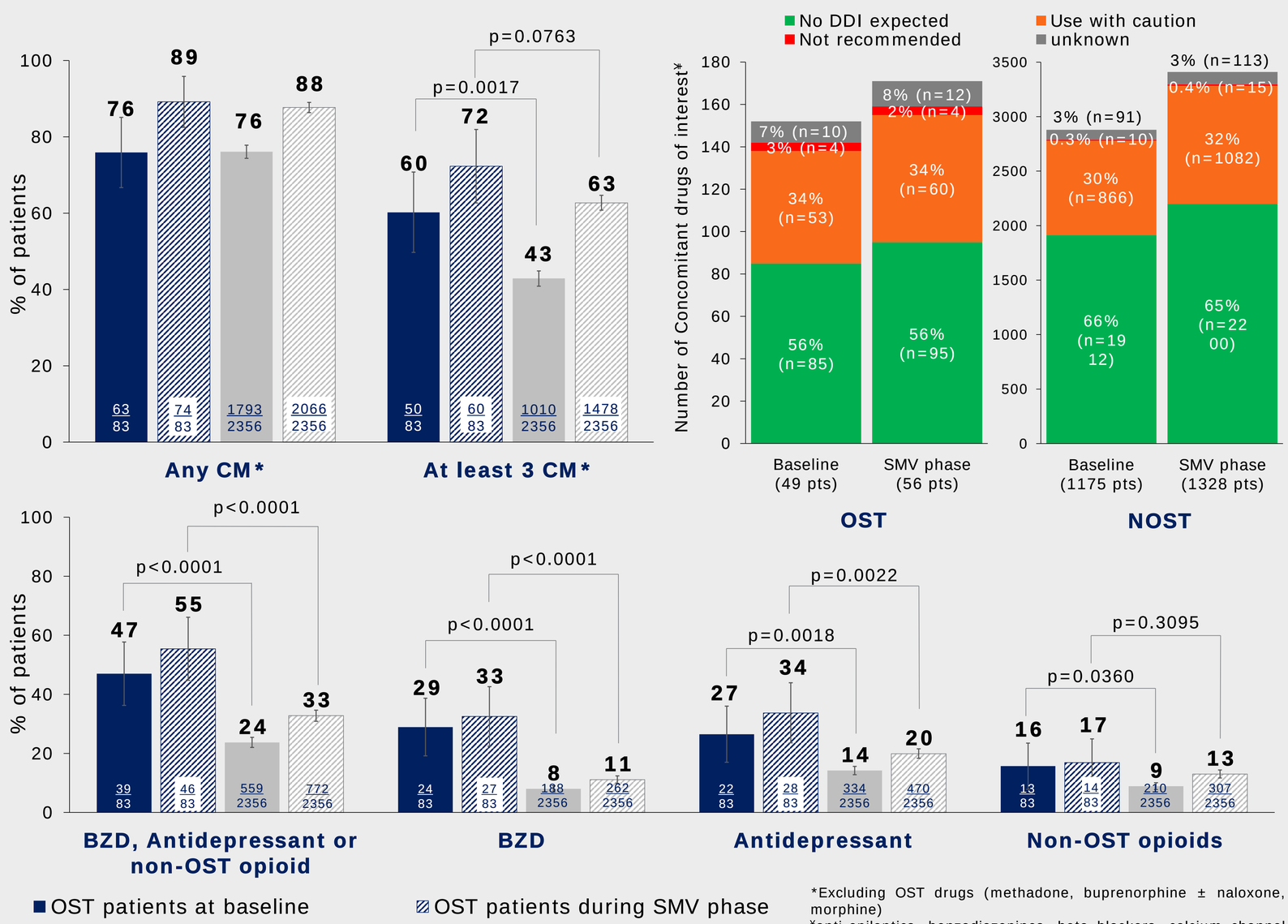
Patients, n (%) with:	OST N=83	NOST N=2356
Any AE	67 (81)	1953 (83)
SAE	6 (7)	63 (3)
Grade 3-4 AE	15 (18)	375 (16)
AE at least possibly related to SMV	39 (47)	1362 (58)
SMV D/C due to AE	3 (4)	34 (1)
Death	1* (1)	1# (<1)

SMV discontinuation (D/C) due to AE in OST patients: rash (N=1, related to SMV), depression (N=1, not related), overdose (N=1; medication error [valium and methadone overdose[3]], not related)

*Considered unrelated to SMV by the investigator (pancytopenia, bradycardia, pyrexia, pneumonia, septic shock, confusional state, dyspnea, and respiratory acidosis)[3] ; #Road traffic accident

In patients on OST, no serious AE (SAE) was deemed SMV-related.

CONCOMITANT MEDICATIONS



*Excluding OST drugs (methadone, buprenorphine ± naloxone, morphine)
¥anti-epileptics, benzodiazepines, beta blockers, calcium channel blockers, other antihypertensives, HIV ARVs, neuroleptics, opioids (non OST), oral antidiabetics, antidepressants, statins
BZD: benzodiazepine

Patients on OST had a baseline median number of CM (excluding the OST drug) of 4 (range 1-15) vs. 3 (range 1-26) for NOST patients. The percentage of patients on OST taking ≥3 CM was higher than in NOST patients (p=0.0017). 8.4% (7/83) of OST patients either changed the OST dose or stopped OST permanently during SMV phase.

CONCLUSION

SMV-containing regimens in OST patients using a substantial number of concomitant medications were well tolerated and resulted in SVR rates similar to those in the general HCV population.

REFERENCES

1. Midgard et al. J Hepatol. 2016; 65(Suppl 1): S33–45; 2. Simeprevir EU Summary of Product Characteristics (2016);
3. Forns et al. Gastroenterology 2014; 146 (7): 1669–1679

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