

Efficacy and safety of sofosbuvir/velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: Analysis of Phase 3 ASTRAL trials

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Abstract

In this post-hoc analysis of the Phase 3 ASTRAL trials [non-opioid substitution therapy (OST), n=984; OST, n=51] evaluating the once-daily, pan-genotypic regimen of sofosbuvir/velpatasvir for HCV infection, OST did not impact completion, adherence, sustained virologic response (SVR12), or safety. SVR12 was 96% (95% CI 87%, >99%) in those receiving OST.

INTRODUCTION

People who inject drugs (PWID) are disproportionately affected by hepatitis C virus (HCV) infection (1). People with a history of injecting drug use includes those having stopped injecting, those with recent injecting, and those receiving opioid substitution therapy (OST, e.g. methadone or buprenorphine), some of whom may also have recently injected drugs. Data are lacking on HCV treatment outcomes with interferon-free direct-acting antiviral agents (DAAs) among people receiving OST, particularly people with genotypes other than HCV genotype 1.

The Phase 3 ASTRAL 1-3 trials evaluated the efficacy and safety of sofosbuvir/velpatasvir in patients with chronic HCV genotypes 1-6 (2, 3). People receiving stable OST were eligible for inclusion, but people with clinically relevant illicit drug use within 12 months or a positive urine drug screen at screening were excluded. No drug screens were performed during or following treatment. These clinical trial populations are highly selected, included people on stable OST, excluded people with recent drug use, and may not be representative of recent PWID populations. However, there are little data on interferon-free DAA therapy among people receiving OST.

The aim of this post-hoc analysis was to evaluate treatment completion, adherence, sustained virologic response (SVR12) and safety of sofosbuvir/velpatasvir in people receiving OST without drug use at screening.

METHODS

Study Participants and Design

From July 18, 2014 to December 19, 2014 participants were enrolled in three international, multicentre, randomized open-label trials, including ASTRAL-1-3, (ClinicalTrials.gov: NCT02201940, NCT02220998, and NCT02201953, respectively) (2, 3). A fixed-dose combination tablet of sofosbuvir/velpatasvir 400 mg/100 mg was administered for 12 weeks in patients with chronic HCV genotypes 1-6. These studies have been described previously (2, 3).

Participants receiving OST were eligible for inclusion in the ASTRAL studies. Patients were excluded if they had clinically significant drug use within 12 months of screening (as assessed by the investigator) or a non-cannabinoids detected by a positive urine drug test during the screening phase not explained by a prescription medication. No drug screens were performed during or following treatment.

Study endpoints

In this analysis, endpoints included treatment completion, adherence ($\geq 90\%$ of doses), SVR12, safety (adverse events [AEs] and serious AEs), and reinfection. The analysis population included all randomized patients who received at least 1 dose of sofosbuvir/velpatasvir. Adherence was calculated by dividing the number of total doses received during therapy (determined by pill counts at all study visits) by the total expected

number of doses. SVR12 was defined as the absence of quantifiable HCV RNA in serum (<25 IU/mL) measured by COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 (Roche Molecular Systems) at 12 weeks after the end of study treatment. All participants were monitored for viral recurrence at 4, 12 (SVR12), and 24 weeks (SVR24) following the completion of treatment. As previously described (2, 3), deep sequencing of HCV NS5A/NS5B was performed for all patients at baseline and at virologic failure to distinguish viral relapse from reinfection.

Statistical analysis

The proportion of participants with treatment completion, $\geq 90\%$ adherence, SVR12, and safety were compared among people receiving and not receiving OST. Comparisons were made using 2-sided Fisher's exact test. All p-values are two-sided; a level of 0.05 was considered statistically significant. Statistical analysis was performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participant characteristics

Of the 1,035 patients enrolled and treated with sofosbuvir/velpatasvir (ASTRAL-1, n=624; ASTRAL-2, n=134; ASTRAL-3, n=277), 51 (5%) were receiving OST at enrolment (67% methadone, 33% buprenorphine). Among people receiving OST (n=51), the mean age was 49 years (SD 10), 76% (n=39) were male, 25% (n=13) had cirrhosis, 22% (n=11) had previous HCV treatment experience, and mean HCV RNA was 6.3 log IU/mL (SD 0.70) (Supplementary Table 1). Among people not receiving OST (n=984), the mean age was 53 years (SD 11), 60% (n=591) were male, 21% (n=207) had cirrhosis, 28% (n=280) had previous HCV treatment experience, and mean HCV RNA was 6.3 log IU/mL (SD 0.70).

Among people receiving OST (n=51), the HCV genotype (G) prevalence was 24% G1a (n=12), 2% G1b (n=1), 16% G2 (n=8), 47% G3 (n=24), and 12% G4 (n=6) (no G5 or G6).

Among people receiving OST and HCV genotype 1 (n=13) and 3 (n=24), 31% (n=4) and 38% (n=9) had cirrhosis. Among people not receiving OST (n=984), the HCV genotype prevalence was 20% G1a (n=198), 12% G1b (n=117), 23% G2 (n=230), 26% G3 (n=253), 11% G4 (n=110), 4% G5 (n=35), and 4% G6 (n=41). Among people not receiving OST and HCV genotype 1 (n=315) and 3 (n=253), 22% (n=69) and 28% (n=71) had cirrhosis.

Study outcomes

The proportion of participants completing HCV therapy was 96% (95% CI 87%, >99%; 49/51) among participants receiving OST, compared to 99.7% (95% CI 99%, >99%; 981/984) among those not receiving OST ($p=0.022$, Supplementary Table 2). The reasons for treatment discontinuation among people receiving OST (n=2) included one participant lost to follow-up and one participant with adverse events (anxiety, headache, and disturbance in attention, discontinued after one dose). The reasons for treatment discontinuation among people not receiving OST (n=3) included one participant lost to follow-up, one participant with lack of efficacy, and one participant with an adverse event (anxiety attack, discontinued after 13 doses).

The proportion of participants with $\geq 90\%$ adherence to therapy was 90% (95% CI 79%, 97%; 46/51) among participants receiving OST, compared to 96% (95% CI 95%, 97%; 946/984) among those not receiving OST ($p=0.06$). Among the five participants with adherence $< 90\%$ among those receiving OST, three participants did not return study drug bottles and

adherence could not be determined (missing bottles were counted as missed doses), one participant discontinued due to adverse events and one participant was lost to follow-up.

The proportion with SVR12 among those receiving OST (96%; 95% CI 87%, >99%; 49/51) was similar to those not receiving OST (98%; 95% CI 97%, 99%; 966/984; $p=0.26$). SVR12 stratified by HCV genotype is shown in Figure 1 and Supplementary Table 3. Of the 2 participants on OST who did not achieve SVR12, one with genotype 2 HCV infection discontinued treatment after one dose of study drug due to AEs and one with genotype 3 infection was lost to follow-up after completing 5 days of treatment. In those receiving OST, SVR was lower in those with <90% adherence compared to those with >90% adherence (60% vs. 100%, $P=0.01$). In those with HCV genotype 3 and cirrhosis ($n=9$), SVR12 was 100% (95% CI 66% to 100%).

The proportion with AEs (86% vs 79%, $p=0.29$) were similar among participants receiving and not receiving OST. The proportion with serious AEs (6% vs. 2%, $p=0.10$) were higher in those receiving OST, but not statistically significant.. AEs were mostly mild or moderate in severity. Serious adverse events in those receiving OST included abdominal pain ($n=1$), bronchitis ($n=1$), and palpitations ($n=1$).

There were no cases of HCV reinfection in the 24 weeks following the end of treatment among participants receiving OST. However, there was one patient not receiving OST that was determined to have HCV re-infection by deep sequencing at time of virologic failure (pre-treatment genotype 3; reinfection genotype 1a).

DISCUSSION

This post-hoc analysis of data from the ASTRAL clinical trials demonstrates that there is no significant difference in SVR12 between people receiving and not receiving OST without recent drug use who received treatment with sofosbuvir/velpatasvir. These findings provide support for current international clinical recommendations advocating for HCV therapy for people receiving OST (4-6).

The comparable SVR12 outcomes in this post-hoc analysis is consistent with previous data of interferon-based HCV therapy (7-9) and interferon-free DAA therapy for chronic HCV genotype 1 among people receiving OST (10-12). However, this study adds considerably to the literature, given that almost all studies of DAA therapy among people receiving OST are restricted to people with HCV genotypes 1, 4 and 6. In this study, the SVR12 was 96% among people receiving OST with chronic HCV genotype 3. This is encouraging, given that a sizable proportion of people receiving OST are infected with this genotype globally (5).

This study has several limitations. People with active drug use at baseline were excluded from participation, and represented a selected population engaged in care. This study did not collect data on injecting drug use or perform urine drug testing during or following therapy. These findings may not be generalizable to other PWID populations (particularly those with recent drug use). The sample size and follow-up duration in this study are limited. Further studies are needed, particularly to characterize reinfection. Lastly, this was a post-hoc analysis that was not specified *a priori*. However, given the paucity of data on DAA treatment outcomes among people receiving OST, these data may provide important information on HCV management in this population.

In conclusion, these data demonstrate that sofosbuvir/velpatasvir is well-tolerated and effective among people receiving OST. This study highlights the importance for further clinical trials with larger sample sizes to evaluate DAA therapy among people with ongoing drug use. Clinical trials are evaluating interferon-free therapy among PWID with recent drug use (SIMPLIFY, NCT02336139; HERO, NCT02824640).

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Conflicts of interest

Jason Grebely is a consultant/advisor and has received research grants from AbbVie, Bristol-Myers Squibb, Gilead Sciences and Merck/MSD. Gregory Dore is a consultant/advisor and has received research grants from Abbvie, Abbot Diagnostics, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Merck, Janssen and Roche. Stefan Zeuzem is a consultant/advisor for Abbvie, BMS, Gilead, Janssen, Merck/MSD. Richard J. Aspinall has received speaker honoraria from Gilead Sciences. Ray Fox is a consultant/advisor for Gilead, Merck, BMS, Abbvie. Graham Foster reports speaker and consultancy fees from Roche, Merck, Gilead Sciences, Novartis, AbbVie, Janssen, Bristol-Myers Squibb, Boehringer Ingelheim, Idenix, Achillion. Alessandra Mangia is a consultant/advisor for BMS, Gilead, Janssen, Merck/MSD, and Roche. Mark Sulkowski is a consultant/advisor for AbbVie, Cocrystal, Gilead, Janssen, Merck, and Trek; serves as the principal investigator for research grants to the Johns Hopkins University from AbbVie, BMS, Gilead, Janssen, and Merck, and payment for the development of educational programs for Clinical Care Option, ViralEd, and DKB. Jordan Feld is a consultant/advisor and has received research grants from Abbvie, Bristol Myers

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Figure 1. Sustained virologic response in patients with chronic HCV genotypes 1-4 receiving and not receiving OST sofosbuvir/velpatasvir in the ASTRAL 1-3 studies.

OST; Opioid substitution therapy.

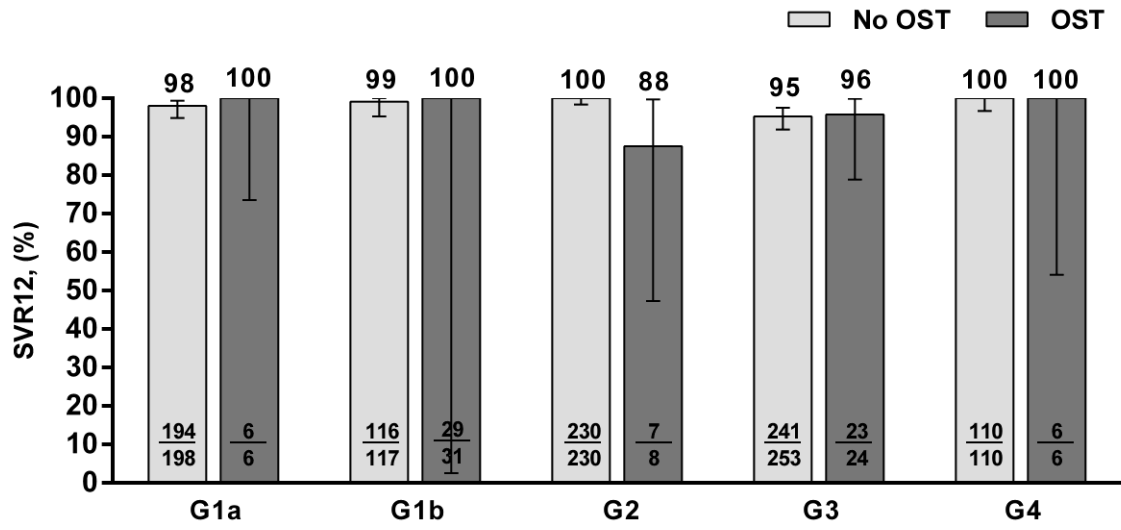
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REFERENCES

1. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nat Rev Gastroenterol Hepatol* 2013;10:553-562.
2. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, Abergel A, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *N Engl J Med* 2015;373:2599-2607.
3. Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, Lawitz E, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *N Engl J Med* 2015;373:2608-2617.
4. AASLD/IDSA. Recommendations for testing, managing, and treating hepatitis C. In; 2015.
5. Grebely J, Robaey G, Bruggmann P, Aghemo A, Backmund M, Bruneau J, Byrne J, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. *Int J Drug Policy* 2015;26:1028-1038.
6. European Association for Study of L. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015;63:199-236.
7. Dimova RB, Zeremski M, Jacobson IM, Hagan H, Des Jarlais DC, Talal AH. Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. *Clin Infect Dis* 2013;56:806-816.
8. Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, Goldberg DJ, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clin Infect Dis* 2013;57 Suppl 2:S80-89.
9. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis. *Clin Infect Dis* 2016;62:683-694.

10. Lalezari J, Sullivan JG, Varunok P, Galen E, Kowdley KV, Rustgi V, Aguilar H, et al. Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. *J Hepatol* 2015.
11. Grebely J, Mauss S, Brown A, Bronowicki JP, Puoti M, Wyles D, Natha M, et al. Efficacy and safety of sofosbuvir/ledipasvir with and without ribavirin in patients with chronic HCV genotype 1 infection receiving opioid substitution therapy: Analysis of Phase 3 ION trials. *Clin Infect Dis* 2016;Submitted.
12. Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, Luetkemeyer A, et al. Elbasvir/Grazoprevir to Treat HCV Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Controlled Trial (C-EDGE CO-STAR). *Ann Intern Med* 2016;In Press.

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