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Eight weeks of sofosbuvir/velpatasvir for genotype 3 hepatitis C in previously untreated patients with significant (F2/3) fibrosis

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Summary

Twelve weeks sofosbuvir/velpatasvir (SOF/VEL) is a highly effective pan-genotypic regimen for hepatitis C. Phase 2 data suggest 8 weeks of treatment may be sufficient for previously untreated noncirrhotic patients with genotype 3 (GT3) infection. To maximize the number of patients potentially cured within a fixed treatment budget, we elected to treat such patients locally eligible for treatment (F2/3), with 8 weeks of SOF/VEL. By local protocol, treatment-naive patients with F2 (LSM > 6.9kPa < 9.5kPa) or F3 fibrosis (≥9.5kPa < 12.5kPa) were eligible for 8-week SOF/VEL treatment. Patients commencing treatment before 1 Oct 2017 were identified from the Scottish HCV database. Baseline and treatment outcome data obtained. Ninety patients were included for analysis (72 (80%) male, mean age 45 (IQR ± 8.4), 28 (31.1%) F3 fibrosis). Opioid agonist therapy (OAT) was prescribed in 82 (91.1%) patients. Of 49 patients attending Glasgow city Alcohol and Drug Services, 27 (55.1%) had evidence of recent drug use (< 3 months) including 8 (16.3%) with self-reported intravenous drug use. On an intention-to-treat basis, SVR rates were 86/90 (95.6%, 95% CI 89.0-98.8). Excluding those who prematurely discontinued treatment (n = 4), died prior to SVR testing (n = 1) or whom experienced reinfection (n = 1), per-protocol SVR rate was 84/84 (100%, 95% CI 95.7-100.0). In conclusion, eight-week SOF/VEL is highly effective in treatment-naive GT3 patients with significant fibrosis. This offers a non-protease inhibitor-based 8-week regimen which may be useful for complex drug interactions or where time-limited opportunity for treatment. In limited resource settings, reduction in drug acquisition costs may help achieve progress towards the goal of HCV elimination.

KEYWORDS

direct-acting antiviral, genotype 3, hepatitis c, NS5A inhibitor, sofosbuvir, velpatasvir

1 | INTRODUCTION

Sofosbuvir/velpatasvir (SOF/VEL) is a highly effective pan-genotypic hepatitis C regimen, with high rates of sustained viral response (SVR) amongst those treated for genotype 3 (GT3) infection.[1] In phase 2 trials, 8 weeks of SOF/VEL was highly effective in treating noncirrhotic patients with GT3[2] but not genotype 1 infection.[3]

Genotype 3 accounts for around half of HCV infections in Scotland. In November 2017, Scottish National HCV guidelines were updated to advocate direct-acting antiviral (DAA) treatment for all patients with HCV. Prior to this, and at the time of the approval of SOF/VEL by the Scottish Medicines Consortium in November 2016,[4] interferon-free DAA regimens for patients with GT3 infection were restricted to those with F2 fibrosis and above, or those with significant extra-hepatic manifestations. Our health board (NHS Greater Glasgow and Clyde) initiates around 40% of hepatitis C treatments in Scotland and allocates a fixed budget for drug costs. This budget is sufficient to meet the Scottish Government minimum treatment targets. However, with judicious spending, more patients may potentially be treated. In order to maximize treatment numbers, and taking into account the available in vitro and phase 2 data, our local HCV treatment guideline committee elected to mandate that treatment-naive noncirrhotic GT3 patients eligible for treatment (F2/3 or F0/1 with significant extra-hepatic manifestations) be treated with 8 weeks of SOF/VEL. Here, we report the results from the initial cohort of patients treated in Glasgow treatment centres using this regimen.

2 | MATERIALS AND METHODS

By local treatment protocol, all treatment-naive patients with F2 or F3 fibrosis commencing treatment from January 2017 received treatment with 8 weeks of SOF/VEL, unless contraindicated, or in the presence of insurmountable drug-drug interactions. For HCV-monoinfected patients, F2 was defined by liver stiffness measurements (LSM) >6.9kPa and <9.5kPa, and F3 by LSM ≥9.5kPa & <12.5kPa. For HIV co-infected patients, the lower cut-offs of ≥6.5 kPa and <8.8 kPa and ≥8.8 kPa and <11.9 kPa were used for F2 and F3 fibrosis, respectively. As is our standard practice for DAAs, SOF/VEL was dispensed via community pharmacies. For patients on opioid agonist therapy (OAT), DAAs were dispensed according to OAT prescription (daily observed therapy (DOT) vs non-DOT).

The Scottish Hepatitis C Database is a national database that holds data on all patients attending HCV services in Scotland, as well as ethics approval for conducting research including on treatment outcome. The database was used to identify all noncirrhotic patients commencing treatment with SOF/VEL, in Glasgow treatment centres, with intended treatment duration of 8 weeks prior to 31st September 2017. Non-GT3 patients were excluded. Baseline data on age, gender, LSM and virological response were obtained. Testing for HCV RNA was carried out by a single laboratory using the Abbot realtime assay, with a lower limit of quantification of 12IU/ml. Where relevant, DAA dispensing data (DOT vs non-DOT) were obtained from pharmacy prescription records. For patients on OAT prescribed by Glasgow City Alcohol and Drug Services, data on history of drug

TABLE 1 Baseline Characteristics and drug use

Demographics	**n = 90**	
Male (%)	72 (80)	
Mean age (SD)	45 (±8.4)	
Fibrosis stage	F0/1 (LSM < 6.9kPa)	2 (2.2)
	F2 (LSM > 6.9 & <9.5kPa)	60 (66.7)
	F3 (LSM ≥ 9.5 & <12.5kPa)	28 (31.1)
Mean LSM (SD)	8.8 (±1.5)	
Mean viral load (SD)	5.7 log iu/ml (±0.9)	
Viral load > 6.77 log iu/ml(6 million)	6 (6.6%)	
Co-infection	HIV	3 (3.3)
	HBV	1 (1.1)
Incarcerated	5 (5.5)	
On OAT	82 (91.1)	
Daily supervised OAT	38 (42.2)	
Drug use for those attending Glasgow City Alcohol and Drug Services[a]	**n = 49**	
Self-reported IV drug use	8 (16.3%)	
Self-reported non-IV drug use	14 (28.6%)	
No self-reported drug use, but positive urine toxicology	5 (10.2%)	
Evidence of drug use (self-reported or urine toxicology)	27 (55.1%)	

Abbreviations: IV, intravenous; OAT, opioid agonist therapy.

[a]Drug use figures were only available for patients attending Glasgow City Alcohol and Drug Services (n = 49).

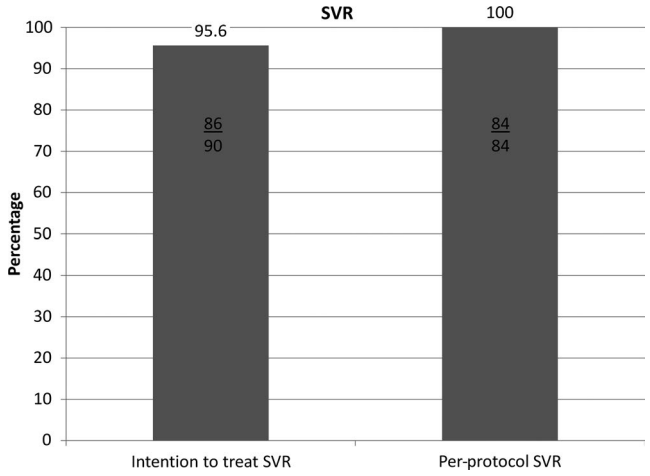

FIGURE 1 Intention to treat and per-protocol SVR rates

use were obtained from the database and augmented by review of community case notes. Self-reported intravenous and nonintravenous drug use were noted, as was unreported drug use evident by positive urine toxicology for nonprescribed drugs of abuse (DOA). Sustained viral response (SVR) was defined by an HCV PCR test less than the lower level of quantification at 12 weeks or more after the end of treatment.

SVR rates were examined on an intention-to-treat basis, comprising every patient meeting the inclusion criteria who commenced treatment. A second per-protocol analysis was undertaken, including only those who completed 8 weeks of treatment as scheduled, and excluding those patients with missing SVR data, or whom experienced reinfection.

3 | RESULTS

Ninety-two patients met the inclusion criteria. Two were subsequently excluded; one with persistent low level viraemia who was unable to be genotyped (successfully treated with 8 weeks of SOF/VEL) and one incarcerated patient who was transferred to another prison where 12 weeks of treatment was given according to local protocol.

Therefore, 90 patients were included in our analysis. Baseline data (Table 1) show a cohort that are predominantly male (80%), and in their 40s (mean age 45 years). Just under one third (28 (31.1%)) had F3 fibrosis. OAT was co-prescribed in 82 (91.1%) patients. Forty-nine (54.4%) were receiving OAT via Glasgow City Alcohol and Drug Services, of whom 27 (55.1%) had evidence of drug use in the 3 months prior to treatment, including 8 (16.3%) with self-reported intravenous drug use.

End of treatment results were available for 82 (91.1%) patients and demonstrated that approximately one in four patients had detectable RNA, either below the level of quantification (16, 17.8%) or quantifiable (7, 7.8%; range 12-41 IU/mL).

Four patients discontinued treatment prematurely. Of these, 2 who discontinued at 6 weeks (early liberation) and 4 weeks (noncompliance) failed to achieve SVR. The other 2 patients, who both discontinued at 6 weeks (1 due to ICU admission and 1 due to noncompliance), achieved SVR. One patient died after the end of treatment of a drug overdose —prior to SVR12 time point. A further patient was negative at the end of treatment but demonstrated low level viraemia at SVR12 point (184 IU/mL) in the context of ongoing intravenous drug use. Further testing was negative beyond SVR 24 time point, and the patient was felt likely to have had reinfection with spontaneous clearance.

On an intention-to-treat basis, SVR rates were 86/90 (95.6%, 95% CI 89.0-98.8). Excluding those who prematurely discontinued treatment, died prior to SVR testing or whom experienced reinfection, the per-protocol SVR rate was 84/84 (100%, 95% CI 95.7-100.0) (Figure 1).

4 | DISCUSSION

Amongst untreated patients with genotype 3 (GT3) infection, 98% of noncirrhotic patients achieved SVR when treated for 12 weeks with SOF/VEL.[1] Such high SVR rates raised the question as to whether shorter treatment durations are possible. Sofosbuvir given in combination with the NS5a inhibitor ledipasvir for 8 weeks has been shown to be highly effective in treating noncirrhotic patients with genotype 1 infection.[5] In vitro, velpatasvir has similar potency against genotype 3 virus (EC_{50} 0.004 nmol[a,6] as ledipasvir has against genotype 1a virus (EC_{50} 0.031 nmol[a7]). In addition, phase 2 data demonstrated high SVR rates amongst noncirrhotic patients with GT3 infection treated for 8 weeks.[2] Specifically, 98.1% (52/53) of GT3 patients treated for 8 weeks with the licensed dose of SOF/VEL (with or without ribavirin) achieved SVR 12, with 1 patient withdrawing consent and no virological failures.

In the light of the available data, we speculated that 8-week SOF/VEL would be an appropriate treatment regimen for noncirrhotic patients. In order to maximize the number of patients treated and cured of their hepatitis C, we took a pragmatic decision to treat for 8 weeks. This off label treatment duration allowed us to treat three patients for the price of two treatments as per the label.

Our results confirm the efficacy of this approach with excellent intention to treat (95.5%) and per-protocol (100%) results, and 8 weeks is now the recommended duration for treatment-naive GT3 patients with F0-3 disease in Scotland.[8] Excellent results in a cohort of patients with significant drug use and high rates of OAT add to the growing body of evidence that current drug use is not a barrier to successful HCV treatment.[9] Two patients achieved SVR after 6 weeks of treatment, one with F2 fibrosis (LSM 8.8 kPa, viral load 6.7 log IU/ml) and one with F3 fibrosis (LSM 10.3 kPa, viral load 6.6 log IU/ml), indicating that for some patients, successful treatment is possible with even shorter durations of therapy. However, a further two patients with abbreviated treatment failed to achieve SVR, one F2 patient with a high viral load treated for 4 weeks (LSM 7.4 kPa, viral load 6.91 log IU/mL) and one F3 patient with HIV co-infection treated for 6 weeks (LSM 11.0, viral load 3.43 log IU/mL). Further

work is required to better characterize those for whom less than 8 weeks of treatment is sufficient to achieve SVR.

Typically, a weakness of real-life cohorts is that of selection bias with uncertainty as to whether clinicians may direct patients with certain characteristics, favourable or unfavourable, towards a particular regimen. In our centres, all treatment-naive GT3 patients with F2/3 fibrosis received 8 weeks of SOF/VEL. Deviation from this regimen was allowed only under exceptional circumstances (such as an insurmountable drug-drug interaction) and required independent review.

One undoubted weakness of our data is that it represents the effects of 8 weeks of SOF/VEL in treating GT3 within a single geographic location. Previous data from our group have demonstrated SVR rates for GT3 infection that are similar to registration trials [10-12]; however, confirmation of our results from additional sites would be welcome. Whilst 90 patients may be viewed by some as a relatively small cohort, it is comparable with the 92 noncirrhotic GT3 patients included in the registration trial for the 8-week regimen of sofosbuvir/velpatasvir/voxilaprevir.[13] Likewise, whilst this cohort was enriched with patients with F2/3 fibrosis (as those with F0/1 were treatment eligible only if significant extra-hepatic manifestations of HCV), the number of patients with F3 fibrosis (28 (31.1%)) may give concern as to the efficacy in this subgroup. These numbers are similar to the 29 GT1 patients with F3 fibrosis treated for 8 weeks with sofosbuvir/ledipasvir in ION-3,[5] leading to an 8-week label and subsequent real world validation of this approach. All of our F3 patients who completed 8 weeks of treatment achieved SVR. Our cohort did contain relatively few patients with a high baseline viral load (>6 million IU/mL) and no patients with a viral load above 10 million IU/mL. Whilst all 5 patients >6 million IU/mL completing 8 weeks of treatment achieved SVR, further data are required to confirm efficacy in this subgroup. After the period presented in this study, the first-line drug choice for genotype 3 patients in our centres changed to an alternative regimen (on cost basis following a national procurement tender process), limiting the ability to accrue more patients. Ongoing procurement rounds will likely lead to further opportunity to report on expanded numbers; however, we feel the current cohort is sufficient to merit dissemination of our results.

Current European and American guidelines recommend 8 weeks of glecaprevir/pibrentasvir or 12 weeks of SOF/VEL as treatment options for GT3 noncirrhotic patients.[14,15] Our real world results add to the phase 2 data suggesting that 8 weeks of SOF/VEL is sufficient for this patient group. Implementation of such an approach would add a non-protease inhibitor-based 8-week regimen to the armamentarium. This may be relevant for individual patients with drug-drug interactions to protease inhibitor regimens. Equally, in situations where there is a time-limited opportunity to treat, or dosing cannot always be reliably provided with food (such as prisons), a further 8-week option may be helpful. For patients who may be in contact with services intermittently or for brief periods of time such as those who are homeless or actively injecting drugs, an 8-week regimen lowers the barrier for treatment. Whilst there is a move towards simplification and use of pan-genotypic regimens, anecdotally genotype is still checked in many countries.

Clinicians may use our data, in combination with phase 2 trials, to draw confidence in an 8-week regimen of SOF/VEL for GT3 infection in treatment naïve patients without cirrhosis. Whilst further data are required for those with high viral loads, our data suggest that an 8-week regimen is applicable to a cohort of unselected patients. Such an approach may be beneficial in treating individual patients, and in some settings, may aid scale up of treatment by lowering the cost of therapy.

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i) A Boyle is guarantor of the article.

ii) A Boyle and ST Barclay were involved in design, data collection, interpretation and preparation of the initial manuscript.

F Marra, E Peters, M Priest, S Datta, M Heydtmann and T Ritchie were involved in critically appraising and revising the manuscript prior to approving the final version.

iii) All authors approved the final version of the manuscript.

CONFLICT OF INTERESTS

A Boyle has served as a speaker for Gilead and Abbvie and has received a grant from Abbvie; F Marra has served as a speaker for Gilead, Abbvie and MSD and has received a grant from Abbvie; E Peters has served as speaker for Gilead and has received a grant from Abbvie; ST Barclay has served as a speaker and advisory board member and has received grants from Gilead and Abbvie. M Priest, S Datta, M Heydtmann and T Ritchie have nothing to disclose.

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