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Tolerability and effectiveness of sofosbuvir and simeprevir in the post-transplant setting: systematic review and meta-analysis

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ABSTRACT

Background: Outcome data on simeprevir and sofosbuvir (SMV+SOF) in patients with liver transplantation (LT) with hepatitis C virus genotype 1 (HCV-1) are limited with individual studies having a small sample size and limited SVR12 (sustained virological response) data. Our goal was to perform a meta-analysis to study the outcome of SMV+SOF ±ribavirin (RBV) in recipients with LT.

Methods: In April 2015, we conducted a literature search for 'simeprevir' in MEDLINE/EMBASE and five major liver meetings. We included studies with SVR12 data in ≥5 post-LT mono-infected HCV-1 patients treated with SMV+SOF±RBV. We used random-effects models to estimate effect sizes, and the Cochrane Q-test (p value <0.10) with I^2 (>50%) to assess study heterogeneity.

Results: We included nine studies with a total of 325 patients with post-LT. Studies included mostly men (59–81%). Pooled SVR12 was 88.0% (95% CI 83.4% to 91.5%). In two studies, HCV-1a patients with mild fibrosis (n=108) had an SVR12 rate of 95.0% (95% CI 82.4% to 98.7%), which was significantly higher than that of HCV-1a patients with advanced fibrosis (n=49) with an SVR12 rate of 81.7% (95% CI 69.8% to 89.5%), OR 4.2 (95% CI 1.1 to 16.1, p=0.03). The most common pooled side effects were: fatigue 21% (n=48/237), headache 9% (n=23/254), dermatological symptoms 15% (n=38/254), and gastrointestinal symptoms 6% (12/193).

Conclusions: SMV+SOF±RBV is safe and effective in recipients with LT with HCV-1 infection.

INTRODUCTION

In the USA, approximately 5000 liver transplantations are performed annually with HCV accounting for approximately 40% of all cases.[1] While liver transplantation is a curative treatment for end-stage-liver-disease (ESLD), HCV recurrence after transplantation is universal in patients who are viraemic prior to transplantation.[2 3] Furthermore, when patients receive immunosuppressive therapy in the post-transplant setting, HCV viraemia may increase and accelerate fibrosis progression. Thus, a significant proportion of recipients with LT (20–30%) progress to cirrhosis within 5 years after transplantation.[2]

Historically, HCV recurrence with genotype 1 has been treated with interferon-based therapies but is associated with poor sustained virological response (SVR) rates (13–43%) and high incidence of treatment-limiting adverse events.[4] Additionally, these trends are even more abysmal in patients with advanced fibrosis who tend to be sicker and more vulnerable to significant treatment side effects.[5] With the recent introduction of first-generation NS3/4 protease inhibitor (PI)-based therapies, SVR rates have greatly improved with up to 60% of patients achieving SVR in this setting;[6 7] however, owing to drug–drug interactions with calcineurin inhibitors and significant adverse events (SAEs), the adoption of these therapies in the post-LT setting has been limited.[6–9]

Recently, all-oral regimens, including simeprevir and sofosbuvir (SMV+SOF), became available for the treatment of patients with pre-transplant with hepatitis C virus genotype 1 (HCV GT1). In the COSMOS study, this regimen demonstrated >95% SVR and had excellent tolerability.[10] While this regimen is an exciting option for the treatment of HCV, there are currently limited treatment and tolerability data of SMV+SOF in the post-transplant setting.

Owing to the limited treatment options in the post-LT setting and sparse published results on SMV+SOF, our goal was to perform a meta-analysis of the available data to estimate pooled SVR rates for SMV+SOF ±ribavirin (RBV) in patients with post-LT.

MATERIALS AND METHODS

Data sources and searches

In April 2015, we comprehensively reviewed the literature by performing the search term, 'simeprevir', in the MEDLINE and EMBASE databases and included studies in

non-English languages. During the review process, we restricted our search to studies with SMV+SOF. We also used the same search term to manually review all abstracts from five major international meetings held during 2014: the American Association for the Study of Liver Disease (AASLD), the Asian Pacific Study of the Liver (APASL), the Digestive Disease Week (DDW), the European Association for the Study of the Liver (EASL) and the World Transplant Congress.

Study selection

Our inclusion criteria were studies with ≥5 post-LT HCV-1 patients treated with SMV+SOF±RBV that had SVR12 data. Our exclusion criteria were studies with patient cohorts which were co-infected with hepatitis B, hepatitis D or HIV. Articles were reviewed independently by two authors (NHN and BEY) and validated by a third (MHN), with discrepancies resolved by a consensus decision.

Data extraction

We used a case report form to collect information on study characteristics (country of origin, practice setting and collaboration), intention-to-treat analysis (ITT), study design (retrospective vs prospective) and baseline patient characteristics, which included ethnicity, age, gender, fibrosis and HCV RNA levels. We also collected baseline treatment information, treatment response (end of treatment response defined as undetectable HCV RNA at the end of treatment) and SVR.

Statistical analyses

Effect sizes were collected as pooled event rates (SVR12) with corresponding 95% CIs using random-effects models and the inverse variance method. For subgroup analyses, we used ORs and corresponding 95% CIs. We used the χ^2-based Cochrane Q-statistic with p≤0.10 and I^2 ≥50% as measures of substantial study heterogeneity in our models. All statistical tests were two sided, with a p value <0.05 considered to be statistically significant. All statistical analyses were performed using Comprehensive Meta-Analysis, V.2 (Biostat, Englewood, New Jersey, USA).

RESULTS

Study search results

We identified a total of 930 articles and abstracts from MEDLINE/EMBASE and 54 abstracts from AASLD, DDW, APASL, EASL and the World Transplant Congress. We removed 182 duplicates and then screened the remaining 802 studies. We identified 39 studies that were assessed for eligibility, of which 30 were removed for various reasons (figure 1). Ultimately, seven abstracts and two full-length articles were included in the qualitative and quantitative analysis.[11–19] The characteristics of these nine studies are described in table 1.

Study and patient characteristics

The primary analysis included 325 recipients with LT with SVR12 data (table 1). The majority were single-centre studies (n=8).[11 12 14–19] All were performed in the USA and included patients with post-LT treated with SMV+SOV±RBV for 12 weeks.[11–19] Two studies directly compared patients with GT1a and stratified by mild versus advanced fibrosis.[13 16] Most patients were Caucasian, had HCV-1a, male, with a mean age of approximately 60 years, and received tacrolimus as part of their immunosuppression (table 1).

SVR12 in patients with post-LT treated with SMV+SOF±RBV

The pooled rate of SVR12 was 88% (95% CI 83.4% to 91.5%) (Q-statistic=8.70, p=0.37; I^2=8.06%) in 325 patients with post-LT (figure 2). There was no difference (p=0.60) in SVR12 rates when comparing studies of a prospective, 88.9% (95% CI 83.5% to 92.6%), versus retrospective, 86.5% (95% CI 76.1% to 92.7%), study design, (p=0.60).

Two studies provided SVR12 and fibrosis data on a total of 108 HCV-1a patients with mild fibrosis and 49 HCV-1a patients with advanced fibrosis.[13 16] Advanced fibrosis was defined as METAVIR F3-F4. There was a trend for a higher SVR12 rate, 93.6% (95% CI 86.8% to 97.0%), in patients with mild fibrosis than in patients with advanced fibrosis, 76.9% (95% CI 62.3% to 87.1%), OR 5.4 (95% CI 0.87 to 33.13; p=0.069) (figure 3).

While some studies reported the use of RBV in combination with SMV+SOF, data were not available for pooled analyses and comparison of SMV+SOF versus SMV+SOF+RBV.

Tolerability of SMV+SOF±RBV

In studies with available tolerability data, the most common pooled side effects were: fatigue 21% (n=48/237), skin symptoms (which included rash, pruritus or photosensitivity) 15% (n=38/254), headache 9% (n=23/254), and GI symptoms (which included nausea or diarrhoea) 6% (n=12/193) (table 2). Data were not available to evaluate the incidence of anaemia in those who received RBV versus those who did not. While data were not available for pooled analysis, the majority of the studies did not report any significant dose reductions, withdrawals secondary to side effects of treatment, or interruption of immunosuppressive therapy.

DISCUSSION

In the post-LT setting, interferon-based regimens are associated with low rates of virological response and high rates of treatment-limiting adverse events.[4 7–9 20] Among recipients with LT with HCV, viral recurrence is universal and associated with a high risk of graft loss and re-transplantation.[1 3] Therefore, there is a need for more effective, better tolerated regimens for patients with post-transplant HCV infection. Given the promising treatment data in patients with non-transplantation from

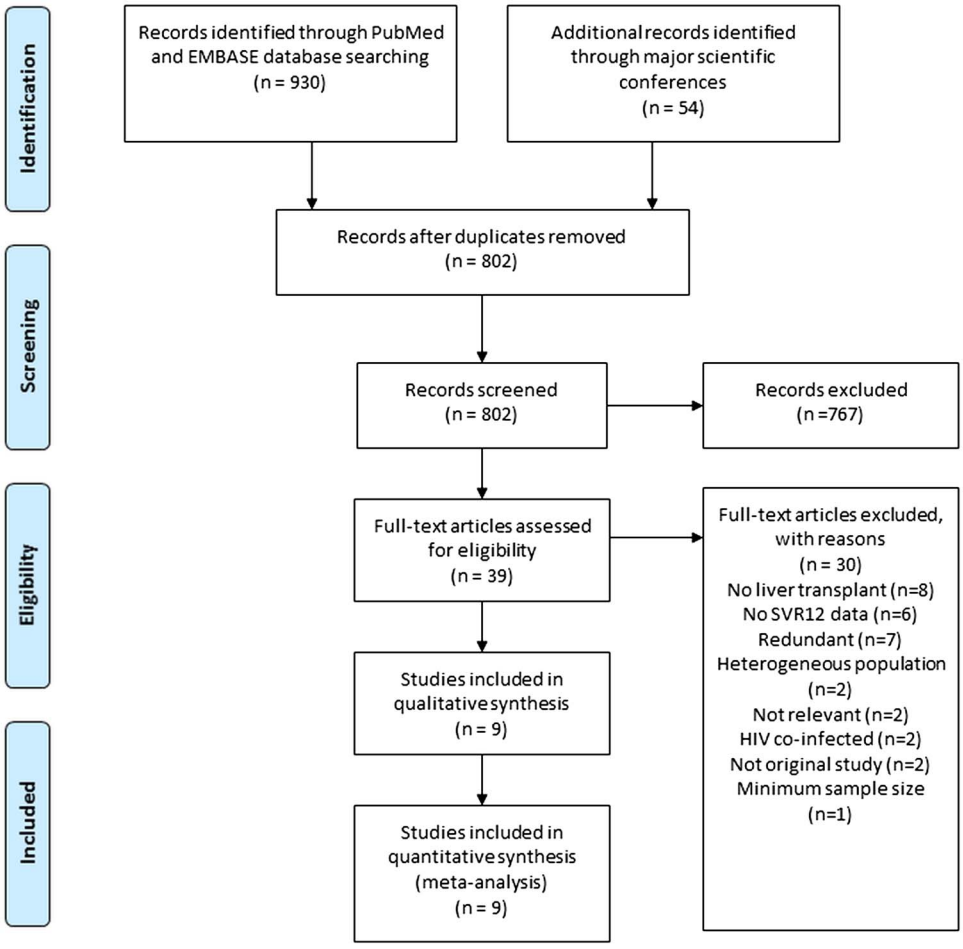

Figure 1 PRISMA flow diagram of included studies (SVR, sustained virological response).

the COSMOS study, SOF+SMV may offer an attractive alternative in the post-LT setting.[10]

In the current meta-analysis, we included nine studies with a total of 325 patients with post-LT who had recurrent HCV GT1 treated with SMV+SOF±RBV. The pooled rate of SVR12 was 88.0% (95% CI 83.4% to 91.5%), which is modestly lower than SVR12 rates in patients with non-LT in the COSMOS study treated with SMV +SOF±RBV (90–94%).[10] The rates were not significantly different between studies that retrospectively enrolled patients compared to those with prospective enrolment, which may reflect the lower discontinuation rates with all oral regimens compared to older interferon-based regimens. Data from the HCV-TARGET network were not included in our study because our primary objective at the time of data collection was to obtain SVR12 data but only SVR4 data were presented at the time. Additionally, data from the recently published article by Saab *et al*[21] were not included, since results from this study were also not available for data collection at the time; however, the SVR rate in this study was 93%, which is similar to our pooled SVR estimate.

In the two studies with available SVR12 and fibrosis data, we observed a trend for a higher SVR12 rate in HCV-1a patients with mild fibrosis, 93.6%, compared to those with advanced fibrosis, 76.9%. The SVR12 result in patients with mild fibrosis was similar to that in cohort 1 (patients with METAVIR F0-F2) of the COSMOS study, while the rate in the advanced fibrosis group was lower than that in Cohort 2 (patients with METAVIR F3-F4) from the same study, which suggests that SMV SOF is not as effective in recipients with LT with advanced fibrosis.[10]

In terms of safety and tolerability, the most commonly identified side effects were fatigue 21% (n=48/237), skin problems 15% (n=38/254), and headache 9% (n=23/254). None of the individual studies reported any significant dose reductions, discontinuations in immunosuppression therapy (which consisted mostly of tacrolimus) and/or treatment discontinuations. In the study by Pungpapong *et al*,[13] approximately 72% of the 25 patients who received RBV developed anaemia that required dose reduction or an intervention. However, additional data from other studies to evaluate the effectiveness and safety of adding RBV versus not adding RBV were not available.

While a majority of studies have yet to be completed and there may be non-significant and significant adverse events to report, the current data from our study suggest that SMV+SOF±RBV is a safe and efficacious treatment

Table 1 Study characteristics*

First author, year	Collaboration	Sample size with SVR12 data	Proportion of genotype 1a (%)	In combination with ribavirin†	Age (years)	Male, N (%)	Advanced fibrosis, N (%)	Median or mean time to post-LT treatment in months or years	Proportion with tacrolimus use (%)
Pungpapong, 2015[13]	Multicentre	105	60	Mix	61.6±6	77 (76)	37 (37)	32 (2–317) months	91
Gutierrez, 2015[16]	Single centre	61	57	Without	60.2±9.3	22 (59)	14 (38)	5.4 years (1.9–8.4)	80
Gordon, 2014[17]	Single centre	15	–	Without	–	–	1 (6)	–	82
Suliman, 2014[11]	Single centre	8	90	Without	62.5	6 (60)	–	–	–
Lutchman, 2014[15]	Single centre	31	64	Without	61.2±7.1	43 (81)	11 (33)	47.0 (1.4–1278.3) months	96
Nair, 2014[14]	Single centre	27	70	With	56±5	28 (61)	19 (41)	0.9±1.6 years	78
Ripper, 2014[12]	Single centre	23	60	Mix	60.9	21 (84)	7 (28)	32.3 (2–215.2) months	76
Crittenden, 2014[19]	Single centre	18	74	Mix	–	–	–	–	–
Ford, 2014[18]	Single centre	37	68	Mix	57	27 (73)	8 (22)	–	62

*Proportions and mean±SD were provided/abstracted from the total number of patients available from each study.
†Classification of studies that included patients: with ribavirin, without ribavirin, or a mix of patients with and without ribavirin.
LT, liver transplantation; SVR, sustained virological response.

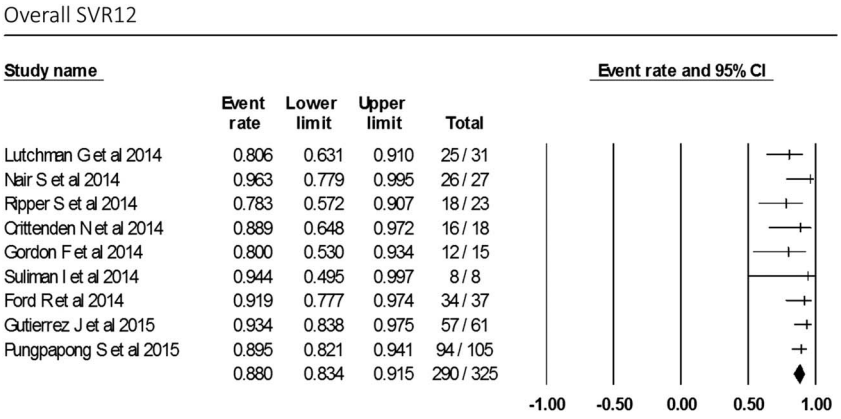

Figure 2 Pooled rate of SVR12 in patients treated with SMV+SOF ±RBV (RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; SMV, simeprevir).

option compared to the older and more recent PI-based therapies.[4 6 20] The improved simplicity and tolerability of this regimen would be expected to enhance patient adherence, increase treatment completion and optimise SVR in real-world settings.[4 6 20]

With the recent introduction of newer and more potent direct-acting agents (DAAs) against HCV, there have been additional new combinations of anti-HCV medications that have given clinicians many more choices in the post-LT setting.[22] In a phase 2 clinical trial with 40 patients (33 patients with genotype 1 and 7 patients with non-genotype 1) treated with SOF+RBV for 24 weeks, Charlton *et al*[23] observed that 67% (n=22/33) of genotype 1 patients achieved SVR12. In a different phase 2 study of 34 genotype 1 patients treated with an all-oral combination of ABT-450/r/ombitasvir, dasabuvir and RBV for 24 weeks, Mantry *et al* observed an SVR12 rate of 97%.[22] The study included 223 patients (221 with genotype 1) who have started treatment and preliminary SVR12 result showed that 93% of the entire cohort achieved SVR12 (n=199/214; 9 patients have yet to reach week 12 post-treatment visit).[22] Recently, a study by Charlton *et al*[24] on ledipasvir+SOF for the treatment of HCV in patients with pre-transplantation and post-transplantation has shown that a high SVR rate can be achieved in patients with post-LT treated for 12 weeks: 96% (n=53/55) in patients without cirrhosis, 96% (n=25/26) in patients with cirrhosis Child-Pugh Class A, 85% (n=22/26) in patients with cirrhosis Child-Pugh Class B, 60% (n=3/5) in patients with cirrhosis Child-Pugh Class C, and 100% (n=4/4) with fibrosing cholestatic hepatitis. While the final results of the studies on SMV+SOF have yet to be completed and published, the results from our current study in a large, diverse patient population in real-world settings can provide clinicians with helpful information on an effective and tolerable treatment option.

Given the different combinations and similar treatment efficacies among the new DAAs, cost becomes an important determinant. Recent base-case analyses of the latest oral regimens compared to previous triple therapy (boceprevir–RBV–pegylated interferon) in patients with genotype 1 non-LT help to provide cost estimates that allow clinicians to make cost-conscious options.[25] Estimates assume that SOF, SMV, daclatasvir and ledipasvir cost $7000, $5500, $5500 and $875 per week, respectively, with results from this study suggesting that SOF-ledipasvir is the most cost-effective for genotype 1 and costs $12 825 more per quality-adjusted life compared to previous triple therapy.[25] However, results from these studies are based on clinical trials and in patients with pre-LT, so additional studies are needed to confirm the cost-effectiveness of this combination when directly compared to SMV+SOF and other SOF-based therapies in the treatment of patients with non-LT.

One of the limitations of our meta-analysis was the small number of studies available, which affected our ability to detect significant publication bias. We also used random-effects models to provide a more conservative estimate for all our analyses. Although most of our data were from observational studies, our findings are more likely to be generalisable to patients in routine clinical settings, since observational studies have broader inclusion criteria for study patients. Furthermore, additional information on SMV+SOF±RBV in the future will

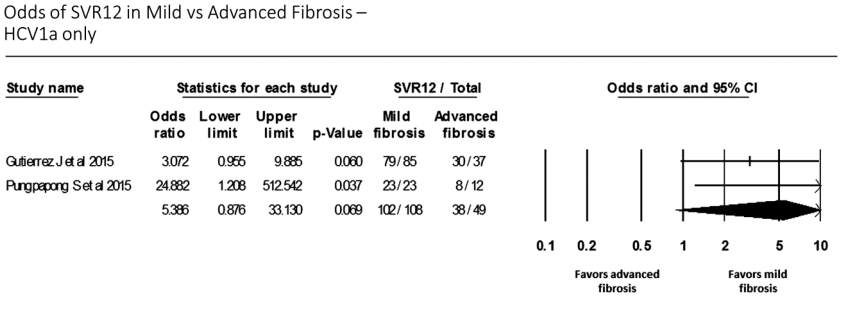

Figure 3 Pooled rate of SVR12 in HCV-1a patients stratified by fibrosis (mild vs advanced) (HCV, hepatitis C virus; SVR, sustained virological response).

Table 2 Pooled side effects*

Side effects	Pungpapong *et al*,[13] n/N (%)	Gutierrez *et al*,[16] n/N (%)	Lutchman *et al*,[15] n/N (%)	Gordon *et al*,[17] n/N (%)	Pooled total, n/N (%)
Fatigue	16/123 (13)	17/61 (28)	15/53 (28)	–	48/237 (21)
Skin problems (rash, pruritus or photosensitivity)	7/123 (6)	7/61 (11)	22/53 (42)	2/17 (12)	38/254 (15)
Headache	6/123 (5)	11/61 (18)	4/53 (8)	2/17 (12)	23/254 (9%
GI symptoms (nausea or diarrhoea)	6/123 (5)	–	2/53 (4)	4/17 (24)	12/193 (6)
Dyspnoea	5/123 (4)	–	–	–	
Insomnia	2/123 (2)	–	10/53 (19)	–	

*Proportions reported in all patients for each study with available side effect data.
GI, gastrointestinal.

mostly be from phase III and IV trials that are currently underway in patients with non-transplantation.[26–28] While there is currently one ongoing phase II trial in recipients with LT (sponsored by Janssen Scientific Affairs, LLC), the planned enrolment is only for 45 patients and data from this cohort will not be available in the immediate future.[29] Lastly, while there are now new data to suggest that 24 weeks of duration is better for patients with post-LT with advanced fibrosis compared to 12 weeks, the data that were available at the time of our analysis did not allow us to compare the treatment effectiveness of SMV+SOF in patients with advanced fibrosis treated for 12 vs 24 weeks.[30] Therefore, given the need for improved therapy in the treatment of HCV in the post-transplant setting, the current meta-analysis provides practitioners with a reasonable estimate of SVR that can be expected with SMV +SOV±RBV in this patient population.

In summary, our meta-analysis represents the first systematic review to report SVR12 data in the post-LT setting for a total of 325 patients from nine individual studies. Data from the current analysis suggest that SMV +SOF±RBV is a highly effective treatment with an SVR rate (88%) and excellent tolerability compared to prior historical therapies. Although limited by the sample size, early data in patients with advanced fibrosis indicate that this treatment option may produce a high probability of cure in similar patients. Given the interim nature of the data, additional studies with SVR12 data are needed to corroborate the findings in our study.

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Contributors NHN contributed to study design, data collection, data analysis and interpretation, drafting of the manuscript. BEY contributed to data collection, data analysis and interpretation, and participation in the drafting of the manuscript. CC contributed to data collection, data analysis and interpretation, and critical review of the manuscript. MJ contributed to data analysis and interpretation and critical revision of the manuscript. GL contributed to critical review of the manuscript. JKL contributed to data interpretation and critical revision of the manuscript. MHN contributed to concept development, study design, data collection, data analysis and interpretation, and critical revision of the manuscript. All authors identified above have critically reviewed the paper and approve the final version of this paper, including the authorship statement. MHN is the guarantor.

Competing interests GL has served as a consultant and as an advisory board member for Gilead Sciences, Jannsen and Abbvie. JKL has received research support from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Glaxo-Smith Kline and Janssen, and has served as a consultant and/or advisory board member for Bristol-Myers Squibb, Gilead, Janssen and Merck. MHN has received research support from and served as a consultant and/or advisory board member for Gilead Sciences, Janssen Pharmaceuticals and Bristol-Myers Squibb.

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