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Original Article

Efficacy and Safety of Sofosbuvir with Simeprevir in Hepatitis C Infected Patients with Severe Chronic Kidney Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background & Aims: Conventional treatment (interferon or ribavirin) for Hepatitis C viral (HCV) infection in patients with severe chronic kidney disease (CKD) has limitations of high dropout and less response rate. Directly acting antivirals raise hopes for HCV treatment in these patients. This meta-analysis was performed to evaluate the evidence for efficacy and safety of sofosbuvir and simeprevir, with or without ribavirin, in HCV-infected patients with severe CKD.

Methods: Data was collected from Medline database, clinical-trial registry sites, and conference proceedings. This meta-analysis screened 78 studies. Quality of studies was assessed by New-Castle Ottawa scale. Heterogeneity and publication bias was checked by chi-square Q test and Eggers' test, respectively. Summary estimate of SVR12 and dropout rate was calculated at 95% confidence interval (CI).

Results: Seven relevant clinical studies were identified. Two case-series and one case-report were excluded; only four studies were eligible for analysis. Three studies were cohort and one was retrospective-cohort in nature. Data was analyzed for 56 subjects. 33/56 subjects had cirrhosis. 39/56 subjects were on hemodialysis. 37/56 subjects were male. 30/56 subjects were treatment-naive. Pooled estimate of SVR12 was found 0.897 (CI 95%=0.957-0.772; p<0.01) and dropout estimate was 0.040 (CI 95%=0.011-0.137; p<0.01). Only one subject discontinued the treatment due to worsening Renal function regardless of ribavirin.

Conclusion: This study concluded that combination of sofosbuvir and simeprevir, with or without ribavirin, was significantly effective and safe in HCV patients with severe CKD. For conclusive results, more data is required as this study involved only limited number of subjects.

Key words: Chronic kidney insufficiency, Efficacy, Hepatitis C, Sofosbuvir, Simeprevir, Safety.

INTRODUCTION

Hepatitis C virus (HCV) infection is an emerging global public health concern with 130-150 million infected people worldwide and 350,000-500,000 HCV-related deaths annually.[1-3] HCV infection manifests not only to cirrhosis, hepatocellular carcinoma, and liver failure but also as several extrahepatic disorders involving Renal, dermatologic, hematologic, and rheumatologic systems.[4]

The risk of HCV infection in patients with end-stage Renal disease (ESRD) undergoing hemodialysis is high mainly due to several routes of transmission thought to stem from the dialysis unit.[5] Moreover, the liver-related morbidity and mortality of HCV appear to be higher in patients with severe Renal impairment.[6] Treatment of HCV infection in severe chronic kidney disease (CKD) with GFR less than 30ml/min/1.73m^2 patients using conventional or pegylated interferon (PEGIFN), with or without ribavirin (RBV), remains a clinical challenge with a low response rate and high dropout rate due to poor tolerability.[7]

The Direct Acting Antivirals (DAAs) for the treatment of HCV infection with severe Renal impairment carry the promises of better safety profiles and higher cure rate. Two DAAs i.e. sofosbuvir and simeprevir were approved in 2013 in the United States and in the first half of 2014 in Europe. Sofosbuvir, a nucleotide analog NS5B polymerase inhibitor, is effective against HCV genotypes 1, 2, 3 and 4 and simeprevir, the third NS3/NS4Aprotease inhibitor is effective against HCV genotype-1.[8]

Higher plasma exposures of sofosbuvir (400 mg) and its inactive metabolite GS-331007 are found in HCV-infected cases with Renal failure since its major elimination route (>81%) is kidney and 15% excretion by feces.[9-10] In contrast, primary route of elimination of simeprevir is feces (>90%) and only a negligible proportion (<1%) takes the Renal route.[11-

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[12] Currently, the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines recommend a standard dose (150 mg) of Simeprevir in patients with CKD stage 4; however, there is lack of evidence for regime containing sofosbuvir and simeprevir in CKD stage 5.[13]

Though a combination of sofosbuvir and simeprevir (SOF+SMV) has been recommended for treatment of genotype-1 HCV infected patients by AASLD and EASL,[14] the safety and efficacy of this regimen in patients with severe Renal impairment or with GFR<30 ml/min/1.73m^2 is unknown. Hence,the treatment of HCV infection in this special population remains a challenge due to the scarcity of evidence on safety and efficacy of DAAs. The results of ongoing clinical studies shall create the evidence on pharmacokinetics, efficacy, and safety of this regimen (SOF+SMV) in HCV patients with severe CKD.

In view of the above, this meta-analysis was conducted by combining available data for an evidence on efficacy and safety of the combination of sofosbuvir and simeprevir, with or without ribavirin, for all clinical results available on patients with Hepatitis C with severe CKD (GFR<30ml/min/1.73m^2).

MATERIALS AND METHODS

Types of studies

We considered all available clinical studies that evaluated efficacy and safety/tolerability of the combination of sofosbuvir and simeprevir with or without ribavirin in hepatitis C patients with severe chronic kidney disease.

Types of participants

We considered studies involving adult patients aged 18 years or more, classified as patients with severe Renal impairment or CKD of stage 4 or 5 in which GFR is equal to or less than 30ml/min/1.73m^2 and less than 15ml/min/1.73m^2, respectively. Both set of participants with ESRD whether on hemodialysis or not, were considered.

Types of interventions

Clinical studies in which sofosbuvir in a dose of 200-400 mg per day and simeprevir in a dose of 150 mg per day with adjusted dose of ribavirin were included.

Search strategy and data extraction

An electronic search of the National Library of medicines' MEDLINE database (Pubmed) was performed and only English studies from 1995 to 2016 were considered. The proceedings of all relevant conferences of the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) congress were searched.

The reference lists of identified trials and major reviews, and trials registered at www.clinicaltrial.gov website were also considered. Monographs of respective drugs were also used.

Only articles, abstracts, and letters were included. Case series and case reports were excluded to reduce publication bias. If duplicate publications were found, the publications with all required information were used.

The key words such as 'chronic', 'hepatitis C', 'HCV infection', 'Renal impairment', 'Renal insufficiency', 'Renal failure', 'CKD', 'chronic kidney disease', 'ESRD', 'end stage Renal disease', 'hemodialysis', 'dialysis','Renal transplantation', 'efficacy', 'sustained virologic response', 'SVR12', 'safety', 'adverse events', 'ADRs', 'ADEs', 'side effects', 'adverse drug reactions', 'sofosbuvir', 'SOF', 'nucleotide NS5B inhibitor', 'simeprevir', 'TMC435', 'SMV', 'sofosbuvir with simeprevir', 'DAAs', 'direct antiviral agents', 'antiviral therapy', 'interferon-free regimen', 'oral therapy', were used.

Inclusion Criteria

Studies on HCV patients aged 18 years or more were included. Treatment regimen with a combination of sofosbuvir and simeprevir, with or without ribavirin, were included in the study. Studies on subjects with severe CKD or GFR<30 ml/min/1.73m^2 were included. Studies that involved patients with or without hemodialysis were included.

Exclusion criteria

Studies with subjects of Renal transplantation, normal Renal function or early stages (1-3) of chronic kidney disease, and studies with duplication, insufficient result information were excluded.

Selection of studies

One author (RS) performed the search to identify potentially relevant studies. Two authors (RS and RA) then independently performed each subsequent step of the selection and review process. The titles and abstracts of identified studies were initially screened for eligibility. Potentially eligible studies were subjected to full-text review for methodological quality assessment (see below) and data extraction (see below). There was no language restriction. Discrepancies were resolved by discussion with two additional authors (PT and AD).

Data extraction

Two authors independently extracted the data and entered in spreadsheet. Data on stage of Renal impairment, hemodialysis, genotypes of Hepatitis C virus, demographic details of subjects, dose of sofosbuvir and simeprevir, its duration, frequency, cirrhosis, design of studies, sustained virologic response at 12th week of end of treatment (SVR12), adverse events, and discontinuation of treatment was collected.

Evaluation of study methodological quality

Newcastle-Ottawa scale (NOS) was used to assess the quality of each study by two authors (RS, RA) independently. Each study was judged on the basis of three broad perspectives which included the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for cohort studies. A star system was used for the calculation in which maximum of one star for each parameter in the domain of selection, exposure and a maximum of two stars for comparability can be awarded.[15] Hence, a maximum of nine stars would be the highest score. Median of score was used as cut off point and studies with score higher than median were considered of higher quality and vice versa.[16]

Outcomes

It included efficacy in which rate of sustained virological response-12 (SVR12) was reported. SVR12 was defined as an undetectable or rapid decline in hepatitis C viral RNA load after 12 weeks of the end of treatment.[17]

Another outcome included safety and tolerability of treatment. It was reported in terms of rate of discontinuation or with drawal of treatment due to adverse drug events.

Data Analysis

Per-protocol analysis was done to calculate response rate of SVR12 and treatment discontinuation. Findings were assessed by both fixed effect model and random effect model.[18-19] Heterogeneity among clinical studies was assessed by using Cochrane Q test and quantified by I^2 value (20). If Q value is greater than the degree of freedom (df) and small p-value

(less than 0.05), it indicates the presence of heterogeneity. The value of I^2 value lies between 0-100% in which value ranges 0-40 show absence of heterogeneity, 30-60 for moderate, 50-90 for substantial and >90 show considerable heterogeneity.[21] Random effect model was used to find pooled estimate effect in the case of heterogeneity between clinical studies and fixed effect model in the absence of heterogeneity.[22,23] Eggers' intercept value was evaluated to check the publication bias and if it deviates from zero and p-value less than 0.1, it shows a symmetry in studies.[24] Funnel plots of standard error by logit event rate and precision by logit event rate were drawn for assessing publication bias.[25] Stratified analysis was performed according to design, dose, and region for SVR12 and dropout rate estimate. Meta-regression analysis was done for checking the co-relation between different co-variates and outcomes. Sensitivity analysis was done to assess the robustness of results of studies. The data was analyzed by using the comprehensive meta-analysis V2 eve (CMA) software. All p-values were two-tailed and p<0.05 was considered as "statistically significant". The present systematic review and meta-analysis was designed and carried out according to standard PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines.[26]

RESULTS

A total of 78 clinical studies were identified and screened after an electronic and manual search by two authors (RS, RA) independently. There were no disagreements regarding the inclusion of clinical studies. After screening and reviewing abstracts, 71 studies were excluded according to exclusion criteria. Seven studies were relevant, of which one case report and two case series were excluded (27-29). Finally, only four clinical studies were included for meta-analysis (Figure 1).

Study and patients' characteristics

Out of four eligible studies, three studies were cohort and one study was a retrospective cohort in nature. It gave information on special population of 56 HCV patients. (30-33) A total of 3 studies were conducted in the USA (Table 1).

All subjects were more than 50 years old. Of the 56, 37 subjects were male. 30 subjects did not receive any HCV treatment in past (56%). In all studies, male subjects were more than 70% except in Saxena's study where female were 74%. At the most, 82% patients were naïve in Nazario's study while least (28%) in Dumortier's study. Two studies (Nazario, Kalyan Ram) were completely conducted on HCV-1 population and another two studies (Saxena, Dumortier) included >55% of the HCV-1 population. 63% (35) subjects were suffering from HCV-1. Cirrhosis was present in 59% (33/56) of subjects in studies and 70% (39/56) subjects were on hemodialysis (Table 2).

All subjects in studies had CKD stage 4 or 5. Studies presented the basic value of HCV-RNA with different variables and found that in three studies (Nazario, Kalyan ram, Saxena) value was greater than 8 million while in one study (Dumortier) information on baseline value of HCV RNA was not available.

Treatment details

Since this meta-analysis included a regime of SOF and SMV with or without RBV, results were adjusted accordingly from the studies. Therapy of SOF and SMV without ribavirin was given in 45/56 of subjects (80%). Treatment duration was not reported in one study and in rest; it was for 12 weeks on an average. Sofosbuvir was found to be given in a dose of 400 mg daily, 400 mg three times a week, and 200 mg daily. Simeprevir was prescribed in a dose of 150 mg daily in all subjects (100%) (Table 3).

Quality assessment results

All studies were found to have NOS score of 6 indicating good quality.

Summary Estimate of Efficacy Outcome (SVR12)

The pooled estimate of SVR12 was 0.897 (event rate = 0.897; 95% CI = 0.957-0.772; p<0.01)(Figure 2). No heterogeneity was found (Q value-1.816, df (Q) = 3, p=0.611, I^2=0). It was found that p-value of Begg's test was 0.73; and 0.021 in Egger's test.The reason for bias could be a small number of studies and low power of tests for such type of meta-analysis.

Efficacy in the form of SVR12 was 100% in half (28/56) of subjects and around 85% in another half. SVR12 was achieved in 93% (28/30) of subjects with a combination of SOF with SMV without RBV. SVR12 rate was similar across all subgroups; and, the highest was with the regime of SOF with SMV (0.906; CI=95% 0.720:0.973). Findings of sensitivity analysis were same with both fixed effect model and random effect model (Table 4).

Summary Estimate of safety outcome

Pooled estimate of discontinuation rate was 0.040 (CI 95% = 0.011-0.137; p<0.01). No heterogeneity was found (Q value – 0.235, df (Q) = 3, p=0.972, I^2=0) (Figure 3). Publication bias was not found (Begg's test, p=1.0, Egger's test = p=0.11).

Discontinuation of treatment or dropout rate because of adverse events of therapy was not found in three studies and 9% (1/11) in one study where adverse events were not reported. Hence, this regime was found tolerable in 98% of subjects and only 2% dropout rate (1/56) among all subjects. The dropout rate was similar across the subgroups and it was least with a combination of SOF with SMV. Findings with both models were similar (Table 5).

Most commonly occurring mild adverse events, which did not require any dose adjustment or hospitalization or with drawal from treatment, were anemia (13, 29%), insomnia (4, 9%), headache (4, 9%), fatigue (10, 22%), nausea (6, 13%), loss of appetite/diarrhea (2, 4%), and rashes (4, 9%). Data was not available on mild adverse events in one study.[33]

Meta-regression analysis and Sensitivity analysis

After performing meta-regression analysis, a significant relationship between any covariate and event rate of SVR12 or between covariate & dropout rate was not found. The reason could be a small number of studies (p>0.05) (Table 6, Table 7). Sensitivity analysis was performed by using leave one out method which showed that findings of included studies were robust. It was assessed for both fixed and random effect model. Overall estimate was the same for both.

DISCUSSION

This meta-analysis is the first for a population of HCV with Renal impairment for regime including direct antivirals (DAAs) i.e. Sofosbuvir with Simeprevir with or without ribavirin. Treatment of hepatitis C using conventional or PEG IFN with or without ribavirin remains a clinical challenge with low response rate, thehigh discontinuation rate due to poor safety and tolerability[7]. Study on treatment of chronic hepatitis C in end stage Renal disease by Duseja *et al* showed that SVR was assessed only in one patient (1/16). Discontinuation of treatment was seen in 37.5% (6/16) patients in which 12.5% was due to worsening of adverse effects and 12.5% was due to unaffordability and 12.5% not responded to the regimen.[34]

A meta-analysis by Fabrizi *et al* on antiviral therapy (pegylated interferon and ribavirin) of hepatitis C in dialysis patients showed an estimate of 0.60 SVR12 pooled estimate and 0.18 of dropout estimate. Among all, 24% dropout were due to anemia and 13% due to infections.[35]

Another study on monotherapy of interferon by Esforzado *et al* showed acure rate of 30-45% in ESRD patients.[36] As therapy of Peg IFN and RBV may cause post transplanted graft rejection, the safety of conventional

Table 1: Demographic data of clinical studies

Authors	Patients (N)	Publication Year	Study Design	Country
Nazario[30]	17	2015	Cohort	USA
Kalyan Ram[31]	15	2015	Cohort	USA
Saxena[32]	13	2015	Cohort	USA
Dumortier[33]	11	2015	Retrospective Cohort	France

Table 2: Clinical data details

Authors.[Ref]	Age (years)	Male (%)	Naïve**	HCV-1(a) (%)	HCV-1(b) (%)	Cirrhosis[$]	HD	eGFR[¥]	HCV-RNA (IU/ml)
Nazario[30]	57(46–69)[#]	82%	82%	76%	24%	47%	88%	<30	>8,00,000[£]
KalyanRam[31]	59.7(7.2)[@]	73%	40%	67%	33%	60%	80%	≤30	9.7×10^{5} [€]
Saxena[32]	60.5(7.5)[@]	28%	NR	42%	21%	75%	28%	≤30	4.4×10^{6}
Dumortier[33]	*	72%	28%	14%	42%	54%	70%	<30	NR

[#] Age in median, [@] Age in mean (Std. error),* ≥65 years in 26% subjects, [¥] Units of eGFR ml/min./1.73m^2, [£] 76% subjects with this baseline HCVRNA level, [€] Mean HCV RNA level, NR- Not reported, □% of patients with hemodialysis, [$] % of patients with cirrhosis, ** % of new patients who never had HCV treatment, Ref-Reference.

Table 3: Treatment and response details

Authors.[Ref]	Regime	Duration	Dose	Efficacy[#]	Dropout rate^
Nazario[30]	Sof + SMV without RBV*	12 weeks	SOF(400 mg) + SMV (150 mg)/daily	100%	0
Kalyan Ram[31]	Sof + SMV without RBV*	12 weeks**	SOF(400 mg) + SMV (150 mg)/daily	87%	0
Saxena[32]	(Sof + SMV) ± RBV*	12weeks	SOF(200 mg) + SMV (150 mg)/daily	85%	6%
Dumortier[33]	(Sof + SMV) ± RBV*	NR	SOF(400 mg)[£] + SMV (150 mg)/daily	100%	0

*Sof-Sofosbuvir, SMV-Simeprevir, RBV-Ribavirin, NR- Not Reported, ** treatment given for 12 weeks in 14 patients and for 24 weeks in one patient, [£] Sof-400mg three times per week, [#] calculated SVR12per protocol analysis, ^ discontinuation of treatment due to adverse events

Table 4: Outcome estimate of SVR12-primary analysis and subgroup analysis

	Fixed effect model Event rate	Q(P)	I^2
N=4	0.897 (0.772:0.957)	1.816	0
Studies only with SOF + SMV (N=2)	0.906 (0.720:0.973)	1.034	3.3
Studies from USA (N=3)	0.885 (0.739:0.954)	1.304	0
Cohort Studies (N=3)	0.885 (0.739:0.954)	1.304	0

SOF-sofosbuvir; SMV-simeprevir; N-total number of studies.

Table 5: Outcome estimate of dropout rate-primary analysis and subgroup analysis

	Fixed effect model Event rate	Q(P)	I^2
N=4	0.051 (0.015:0.156)	0.738	0
Studies only with SOF + SMV (N=2)	0.029 (0.004:0.182)	0.004	0
Studies from USA (N=3)	0.040 (0.009:0.158)	0.234	0
Cohort Studies (N=3)	0.040 (0.009:0.158)	0.234	0

SOF-sofosbuvir; SMV-simeprevir; N-total number of studies.

Table 6: Meta-regression for co-relation between covariates and SVR12

Covariate	Regression Coefficient	Standard error	95% CI	Z-value	p-value
Cirrhosis	-5.05	4.44	-13.8;3.66	-1.14	0.225573
Hemodialysis	1.33	1.89	-2.37;5.04	0.71	0.47959
HCV-1	-0.008	2.87	-5.63;5.62	-0.003	0.99770
Size of Study	0.37	0.32	-0.25;0.99	1.17	0.24284
Dose of SOF	-0.00013	0.005	-0.01; 0.01	-0.03	0.97898
Dropout Rate	-0.08	0.11	-0.29;0.14	-0.70	0.48512
Male	0.02	0.02	-0.024;0.058	0.79	0.42951
Naive	2.25	3.44	-4.49;8.99	0.65	0.51380

Table 7: Meta-regression for co-relation between covariates and Dropout rate

Covariate	Regression Coefficient	Standard error	95% CI	Z-value	p-value
Cirrhosis	3.91	4.96	-5.81;13.6	0.79	0.43081
Hemodialysis	-2.08	2.43	-6.84;2.67	-0.86	0.39100
HCV-1	-1.93	3.65	-9.09;5.23	-0.53	0.59635
Study Size	-0.15	0.31	-0.77;0.47	-0.48	0.63382
Dose of SOF	0.003	0.006	-0.01;0.02	0.45	0.65329
Male %	-0.02	0.03	-0.07;0.03	-0.85	0.39667
Naive	-0.65	3.58	-7.67;6.38	-0.18	0.85650

Table 8: Demographic and clinical details of Case series

Authors.[Ref]	Age (years)	Male (%)	Naïve	HCV-1 (%)	Cirrhosis	HD	eGFR	HCV RNA (IU/ml)
Hundermer[27]	60±14	83%	50%	100%	50%	33%	<30	2.99×10^6
Singh[29]	56.8±20	25%	87.5%	87.5%	37%	100%	<30	4.2×10^5

Ref-Reference; HD-hemodialysis; GFR-Glomerular Filtration Rate.

Table 9: Treatment and response details of Case series

Authors.[Ref]	N	Regime	Duration	Dose	Efficacy	Dropout rate
Hundermer[27]	3	Sof + SMV without RBV	12 weeks	SOF(400 mg) + SMV (150 mg)/daily	(2/3) 67%	0
Singh[29]	4	Sof + SMV without RBV	12 weeks	SOF(400 mg) + SMV (150 mg)/daily	100%	0

Ref-Reference; SOF-sofosbuvir; SMV-simeprevir; RBV- ribavirin; N-total number of subjects.

treatment remains an issue to address[37,38] The rapid evolution of interferon-free regimen DAAs changed the perception about the treatment of chronic HCV in difficult to treat group. Difficult to treat group included HCV patients with severe Renal impairment including ESRD or kidney transplantation.[39] However, efficacy and safety of newer HCV therapies remain to be confirmed in this special population. The purpose of this meta-analysis is to create evidence by compiling all available results for efficacy and safety for this particular combination that can be helpful for making strong recommendations for such population.

Presently, clinical studies are in progress for DAAs but strong recommendations are not available for the population of HCV with severe Renal impairment yet. Hence, this meta-analysis involved all type of sources for getting information on this combination including conference proceedings, available databases, trial registry sites as well as abstracts with complete information on required variables but excluded case report[28] and case-series[27,29] to avoid publication bias and heterogeneity. These case series also showed the results for safety and efficacy of regime of SOF+SMV without RBV for this special population. Case series by Hundermer *et al* was retrospective and case series by Singh *et al.* was acohort in nature (Table 8). Results showed significant SVR 12 response and no discontinuation due to treatment. Patients suffered from mild adverse events but not severe which could cause a dropout (Table 9).

Findings showed the SVR12 and dropout event rate of 0.897 & 0.05, respectively, with the regime of sofosbuvir with Simeprevir with or without ribavirin in HCV patients with severe chronic kidney disease. Even, SVR12 with a combination of sofosbuvir and Simeprevir without ribavirin was found more significant, 0.91 and 0.04, respectively; there was no case of dropout.

Among all included studies, only one patient had discontinued the treatment due to worsening of Renal function. However, a causal relationship with ribavirin could not be found. In rest of the cases, all adverse events were mild which included anemia, insomnia, headache, nausea, fatigue, diarrhea, loss of appetite, and rashes or itching. These adverse events did not require any hospitalization and any dose adjustment.

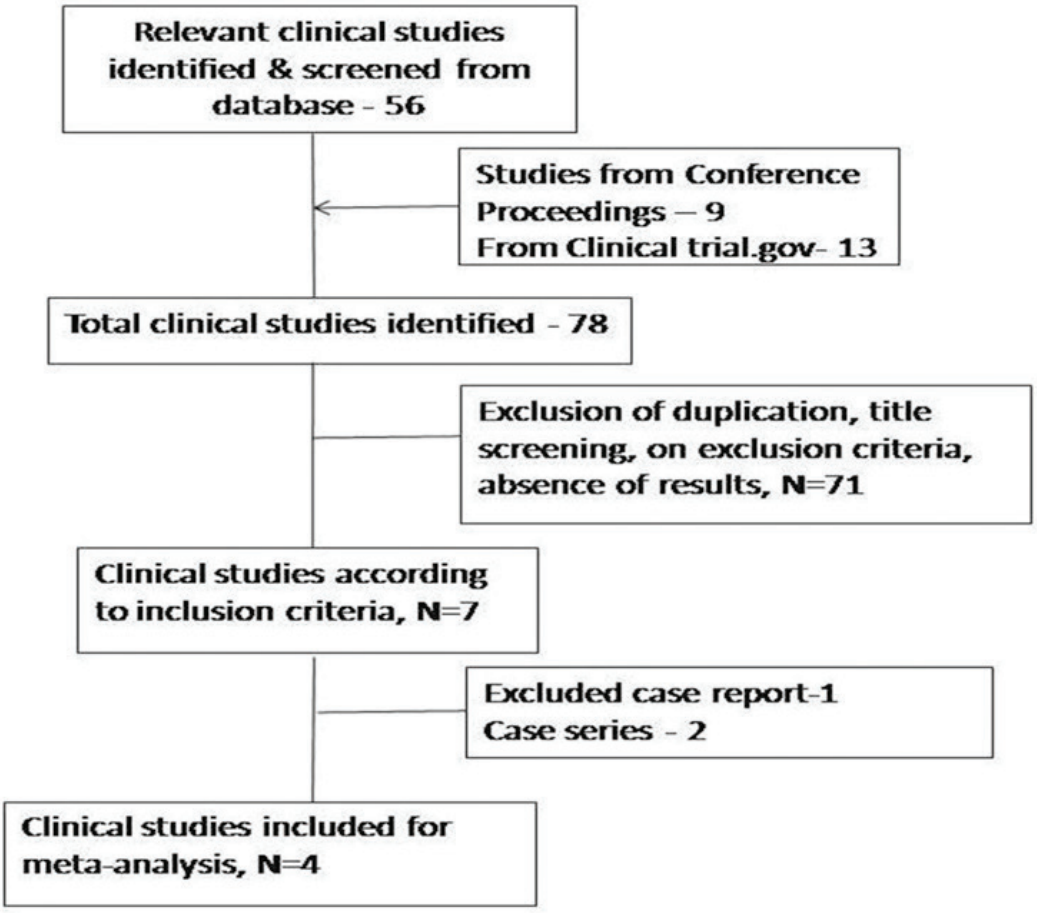

Figure 1: Flowchart of Screening of Studies.

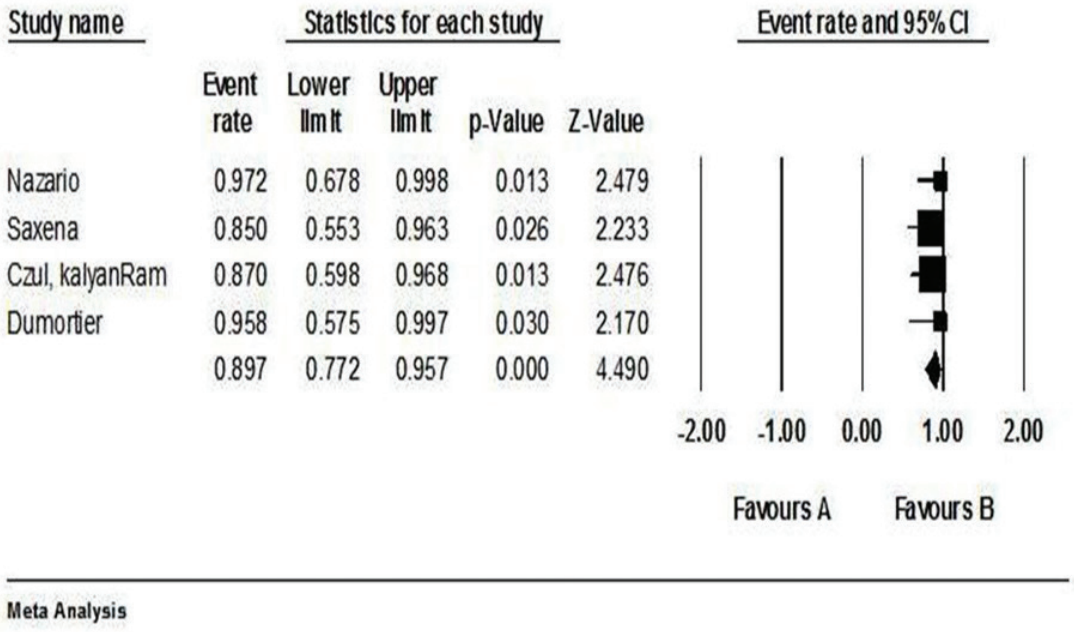

Figure 2: Summary Estimate of SVR12 Outcome.

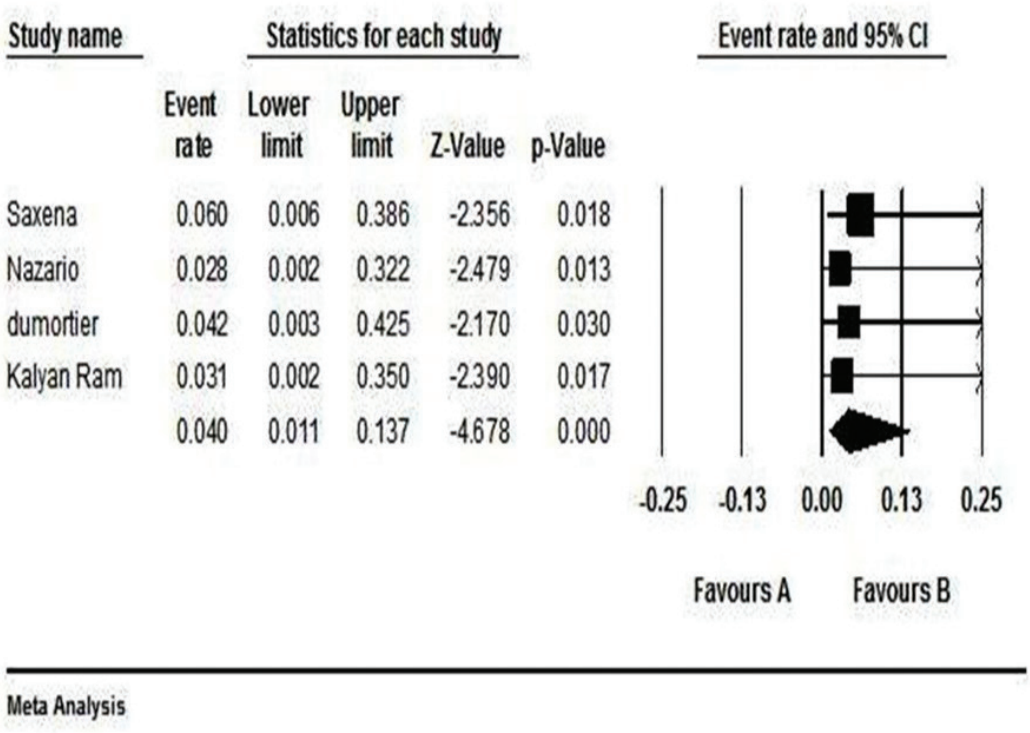

Figure 3: Summary Estimate of Discontinuation rate.

Limitations of the present study involve small sample size, limited clinical studies, absence of histological data, and no information on dose and dose adjustments of ribavirin. Data was not available on correlation between the dose of sofosbuvir and outcome.

CONCLUSION

This meta-analysis showed significant SVR12 response with a combination of sofosbuvir and simeprevir with or without ribavirin and even better outcome estimate with a combination of sofosbuvir and simeprevir without ribavirin. Since sample size of the current study is very less for the strong recommendation of this combination for HCV patients with severe Renal impairment, further prospective research is required. At present, from all available evidence, it was concluded that combination of sofosbuvir and Simeprevir with or without ribavirin is efficacious, safe, and tolerable in HCV patients with severe chronic kidney disease.

List of Abbreviations

HCV: Hepatitis C Virus; **CKD:** Chronic Kidney Disease; **SVR:** Sustained Virologic Response; **DAAs:** Direct Acting Antivirals; **ESRD:** End Stage Renal Disease; **AASLD:** American Association of Liver Diseases; **IDSA:** Infectious Diseases Society of America; **EASL:** European Association of Study of Liver; **GFR:** Glomerular Filtration Rate; **SOF:** Sofosbuvir; **SMV:** Simeprevir

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