Epclusa®, Harvoni®, Sovaldi®, Vosevi®: Renal Safety

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The following document presents available data regarding the renal safety of sofosbuvir-based regimens, such as Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]), Harvoni® (ledipasvir/sofosbuvir [LDV/SOF]), Sovaldi® (sofosbuvir [SOF]), and Vosevi® (sofosbuvir/velpatasvir/voxilaprevir [SOF/VEL/VOX]).

Summary

Product Labeling

According to the US Prescribing Information for LDV/SOF, SOF/VEL, and SOF/VEL/VOX, no dosage adjustment is recommended in patients with any degree of renal impairment, including patients requiring dialysis.[1-3]

No dosage adjustment of SOF is required for patients with mild or moderate renal impairment. The safety of efficacy of SOF has not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or ESRD requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.[4]

Refer to RBV tablet prescribing information for RBV dosage modification for patients with CrCl ≤50 mL/min.[1-4]

Prospective Clinical Data

Two prospective studies evaluated the effects of DAAs, including SOF-based regimens, on renal function during and after treatment. SVR12 was achieved in approximately 98% of participants. SOF-based treatment was associated with varying eGFR effects, including improvements in eGFR and worsened renal function compared to other DAA treatments.[5,6]

Retrospective Clinical Data

The effect of HCV treatment on renal function in patients who received DAAs such as SOF-based regimens was evaluated across 5 retrospective studies that ranged from a single-center chart review to a review of 75 phase 2 and phase 3 studies,. Study results showed varied outcomes in renal function (assessments included eGRF, SCr, and NGAL). Studies showed that renal function improved, remained stable, or decreased renal function during treatment.[7-11]

The full indication, important safety information, and boxed warnings are available at:

https://www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.pdf;
https://www.gilead.com/-/media/files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf;
https://www.gilead.com/-/media/files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf;
https://www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vosevi/vosevi_pi.pdf.

Prospective Clinical Data

Prospective Cohort Study[5]

Study Design and Demographics

Coppola et al conducted a prospective cohort study at 3 centers in Italy between March 2015 and December 2017 to determine the effect of DAAs on renal function and factors that mitigated or worsened renal function. DAA selection was determined by international guidelines and treatment availability, and only those with all $eGFR_{CKD-EPI}$ measurements (at baseline, after Month 1, at the EOT, and SVR12) were included in the study. LDV/SOF ± RBV (33.7%; 136/403), and PrOD ± RBV (30.3%; 122/403) were the most frequently used DAA regimens.

Table 1. Baseline Demographics and Disease Characteristics (Coppola et al)[5]

Key Demographics and Characteristics	Overall (N=403)	eGFR >90 (n=162)	eGFR 60-89 (n=173)	eGFR 30-59 (n=62)	eGFR <30 (n=6)	*P*-value
Age, median (IQR), years	69 (61-75)	64 (53-71)	71 (64-75)	73 (68-77)	75 (67-79)	<0.001
Male, n (%)	203 (50)	82 (51)	106 (61)	13 (21)	2 (33)	<0.001
eGFR, median (IQR), mL/min/1.72 m^2	84.9 (70.8-97.3)	101 (94.5-111.2)	77.1 (72-84.3)	51.6 (44.9-56.2)	25.5 (19.4-29.7)	<0.001
HCV RNA, median, IU/mL	1,241,955	1,228,338	1,380,000	1,024,650	542,785	0.5
GT						
1a, n (%)	25 (6)	15 (9)	8 (5)	1 (2)	1 (17)	0.08
1b, n (%)	280 (70)	110 (68)	124 (72)	41 (66)	5 (83)	0.69
2, n (%)	67 (17)	21 (13)	29 (17)	17 (27)	0	<0.05
3, n (%)	25 (6)	14 (9)	8 (5)	3 (5)	0	0.39
4, n (%)	6 (2)	2 (1)	4 (2)	0	0	0.59
MELD, median (IQR)	7 (7-9)	7 (7-9)	7 (7-8)	7 (7-11)	14 (8-21)	<0.05
Cirrhosis, n (%)	145 (36)	52 (32)	57 (33)	30 (48)	6 (100)	<0.01
Child-Pugh B, n (%)	46 (11)	14 (9)	15 (9)	14 (23)	3 (50)	<0.01
Prior HCC, n (%)	13 (3)	6 (4)	6 (4)	0	1 (17)	0.16
TE with IFN, n (%)	196 (49)	84 (52)	78 (45)	31 (50)	3 (50)	0.66

Abbreviation: HCC=hepatocellular carcinoma.
Note: *P*-values represent comparisons between eGFR stages.

Efficacy

Overall, SVR12 was achieved by 98% of all participants (395/403). SVR12 was achieved in 98.2% of the 335 participants without CKD, in 98.4% of the 62 participants with eGFR 30-59 mL/min/1.73 m^2, and in 83.3% of the 6 participants with eGFR <30 mL/min/1.73 m^2.

Changes in eGFR

Renal function significantly improved from baseline to SVR12 in all participants (median eGFR: 84.5 vs 88.1 mL/min/1.72 m^2; *P*<0.05). Achievement of SVR12 was associated with an improvement in median (IQR) eGFR from baseline to the SVR12 time point: SVR12 achievers (n=395), +3.7 mL/min/1.72 m^2 (-12.1, +22.8; *P*<0.05). Participants without CKD and who did not achieve SVR12 did not have significant changes in eGFR. Participants with Child-Pugh B cirrhosis had significant improvements in eGFR from baseline to SVR12 (71.1 mL/min/1.72 m^2 vs 79.5 mL/min/1.72 m^2; *P*<0.001). Analysis by DAA treatment received showed that improvements from baseline to SVR12 were observed in only those who received SOF-based or non-RBV-based treatment (Table 2). However, renal function was significantly improved in each of the DAA subgroups analyzed among the 68 participants with an eGFR <60 mL/min/1.73 m^2 (Table 2).

Table 2. Changes in eGFR from Baseline to SVR12 by DAA Regimen Overall and in Those with CKD (Coppola et al)[5]

DAA Regimen	All Participants			Participants with CKD (n=68)		
	n	Change from Baseline to SVR12 (median [IQR], mL/min)	*P*-value	n	Change from Baseline to SVR12 (median [IQR], mL/min)	*P*-value
SOF-based	280	+4.3 (-10.0, +21.5)	<0.01	52	+37.3 (+4.5, +48.5)	<0.001
Non-SOF-based	123	+1.9 (-15.9, +24.0)	0.26	16	+30.7 (+16.7, +52)	<0.01
RBV-based	185	+2.0 (-13.8, +23.9)	0.29	28	+37.2 (+9.8, +54.1)	<0.001
Non-RBV-based	218	+4.9 (-9.3, +22.4)	<0.05	40	+35.7 (+4.3, +50.4)	<0.001
Non-SOF/RBV-based	61	+2.5 (-14.3, +22.9)	0.48	20	+29.7 (-0.8, +51.4)	<0.05

An improvement in baseline eGFR of ≥+10 mL/min/1.72 m^2 was observed in 148 participants overall and in 49 of participants (72.1%) with CKD. Among these participants, SOF-based treatment (hazard ratio: 1.56; 95% CI: 1.05-2.32; *P*<0.05), compensated, and decompensated cirrhosis were each associated with renal function improvement after adjusted univariate analysis, while each 1-year increase in age was associated with a decline in renal function.

Prospective Clinical Study[6]

Study Design and Demographics

Liu et al conducted a prospective study in 481 participants with compensated liver disease and baseline eGFR ≥30 mL/min/1.72 m^2 who received SOF-based or SOF-free HCV treatment to compare changes in renal function (as assessed by $eGFR_{CKD-EPI}$) from baseline to SVR24. Participants who received HCV treatment between February 2015 and July 2018 from 2 centers in Taiwan were enrolled. Assessments of eGFR were conducted at on-treatment Weeks 1, 2, 4, 6, 8, and 12, and post-treatment Weeks 4, 8, 12, and 24. The proportion of participants taking concomitant nephrotoxic drugs (ie, aspirin, NSAIDs, β-lactams, quinolones, ACEIs, ARBs, loop diuretics, and thiazides) was similar between groups (*P*>0.05, for each).

Table 3. Baseline Demographics and Disease Characteristics (Liu et al)[6]

Key Demographics and Characteristics	SOF-Based Therapy (n=308)	SOF-Free Therapy (n=173)	*P*-value
Age, mean (SD), years	55 (14)	59 (12)	0.004
Male, n (%)	180 (58)	90 (52)	0.18
Concomitant diseases, DM/HTN, n (%)	53 (17)/67 (22)	38 (22)/61 (35)	0.23/0.002
HCV RNA, mean (SD), log_{10} IU/mL,	6 (1)	6 (0.8)	0.84
>6,000,000 IU/mL, n (%)	66 (21)	17 (10)	0.003
HCV GT 1, n (%)	143 (46)	158 (91)	<0.001
Cirrhosis (Child-Pugh A), n (%)	76 (25)	58 (34)	0.03
+ RBV, n (%)	51 (17)	5 (3)	<0.001
eGFR (by $eGFR_{CKD-EPI}$), mean (SD), mL/min/1.73 m^2	88 (21)	87 (20)	0.62
CKD Stage			0.79
Stage 1 (≥90 mL/min/1.73 m^2), n (%)	166 (54)	89 (51)	N/A
Stage 2 (60-89 mL/min/1.73 m^2), n (%)	107 (35)	61 (35)	
Stage 3 (30-50 mL/min/1.73 m^2), n (%)	35 (11)	23 (13)	
DAA regimen			
SOF/VEL, n (%)	174 (56)	-	N/A
LDV/SOF, n (%)	93 (30)	-	
SOF + DCV, n (%)	26 (8)	-	
SOF + RBV, n (%)	15 (5)	-	
PrOD, n (%)	-	120 (69)	
Grazoprevir/elbasvir, n (%)	-	32 (18)	

Glecaprevir/pibrentasvir, n (%)	-	21 (12)	

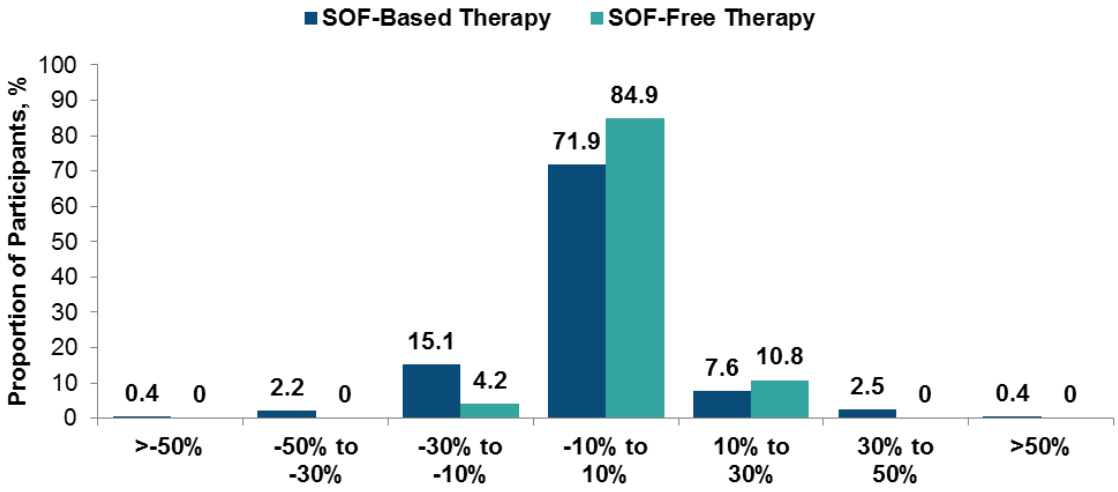
Efficacy and Changes in eGFR

SVR12 was achieved by 98.1% of those who received SOF-based treatment and 98.3% of those who received SOF-free treatment. Six participants were lost to follow-up and did not have SVR12 reported.

A majority of participants experienced eGFR changes ±10% from baseline at SVR24 (SOF-based, 71.9%; SOF-free, 84.9%). Participants who received SOF-free treatment had significantly greater eGFR changes from baseline to SVR24 (see Figure 1; *P*=0.001) and changes in eGFR were observed as early as Week 12 (*P*<0.001).

Overall, from baseline to SVR24, the adjusted slope coefficient difference for SOF-based therapy was associated with an eGFR decrease of -0.33 mL/min/1.73 m^2 per month (*P*<0.001). Decreases in eGFR were mainly observed during SOF treatment (-1.24 mL/min/1.73 m^2 per month; *P*<0.001) and increases in eGFR were observed after SOF treatment completion (0.14 mL/min/1.73 m^2 per month; *P*=0.004).

Figure 1. eGFR Changes from Baseline to SVR24 (Liu et al)[6]



An unadjusted GLMM generalized linear mixed-effect model showed that increasing age (per 1-year increase), concomitant DM (present vs absent), HTN (present vs absent), SOF-based therapy (vs SOF-free), CKD Stage 2 (vs Stage 1), and CKD Stage 3 (vs Stage 1) were independently associated with a significantly decreased slope coefficient difference (*P*≤0.001, for each). Adjusted GLMM analysis showed that only increasing age, SOF-based therapy, CKD Stage 2, and CKD Stage 3 were independently associated with a significantly decreased slope coefficient difference (*P*<0.001, for each). An unadjusted analysis of on-treatment (baseline to EOT) slope coefficient differences of eGFR via a GLMM revealed that increasing age, concomitant DM, HTN, HCV RNA (>6,000,000 vs ≤6,000,000 IU/mL) each revealed significant decreases in eGFR (*P*≤0.01, for each); however, after adjustment, only increasing age was associated with a significant decrease in eGFR (*P*<0.001). Similar results were observed for off-treatment (from EOT to SVR24) unadjusted GLMM analyses, with increasing age, concomitant DM, and concomitant HTN each being associated with decreased eGFR (*P*<0.001, for each). After adjustment of the GLMM, only increased age was associated with decreased eGFR (*P*<0.001).

Retrospective Clinical Data

Retrospective Review of Phase 2 and Phase 3 Studies[7]

Study Design and Demographics

Thirty-seven phase 2 and 38 phase 3 trials, which studied LDV/SOF, SOF/VEL, and SOF/VEL/VOX treatment, were retrospectively assessed to determine the safety of SOF-based treatment in patients with normal ($eGFR_{CG}$ >80 mL/min/1.73 m^2), mild (50-80 mL/min/1.73 m^2), or moderate (30-49 mL/min/1.73 m^2) renal function. Study authors stratified results by

compensated and decompensated liver disease. RBV was added to 51% of all patients' regimens. Key demographics and characteristics are summarized in Table 4.

Table 4. Baseline Demographics and Disease Characteristics by Liver Disease Status (Sulkowski et al)[7]

Key Demographics and Characteristics	Non-Cirrhotic and Compensated Cirrhosis			Decompensated Cirrhosis		
	Normal Renal Function (n=12,849)	Mild Renal Function (n=2,774)	Moderate Renal Function (n=179)	Normal Renal Function (n=457)	Mild Renal Function (n=287)	Moderate Renal Function (n=56)
Age, mean, years	51	60	64	56	61	62
Male, %	68	44	51	80	55	46
White/Black/Asian, %	76/8/14	62/8/28	71/8/17	81/5/11	77/7/14	80/9/11
HCV RNA, mean (SD), IU/mL	6.3 (0.72)	6.3 (0.72)	6.3 (0.66)	5.8 (0.74)	6 (0.66)	5.9 (0.7)
HCV GT 1, %	49	58	78	80	88	86
TE, n (%)	69	39	51	71	62	62
Cirrhosis, %	26	22	23	-	-	-
ALT, mean, U/L	85	67	56	67	66	66
Baseline eGFR, median (IQR), mL/min/1.72 m^2	118.7	69.4	43.8	112.7	65.8	43.3
eGFR at post-treatment Week 4, median (IQR), mL/min/1.72 m^2	115.4	70.6	46.4	110.3	68	48.9

Efficacy and Safety

During treatment, through post-treatment Week 4, and irrespective of cirrhosis status, eGFR measurements remained stable among those with normal, mild, and moderate renal impairment. Thirty-four patients with moderate CKD had eGFR fluctuations ≥10 mL/min/1.73 m^2, including 11 who had a decrease in eGFR, 22 had an eGFR increase, and 1 who had an eGFR increase and decrease. Similar AE rates were observed in those with normal, mild, and moderate renal impairment regardless of cirrhosis status (Table 5).

Table 5. Renal AEs by Renal Function Subgroup and Liver Disease Status (Sulkowski et al)[7]

Renal Safety Parameters	Non-Cirrhotic and Compensated Cirrhosis			Decompensated Cirrhosis		
	Normal Renal Function (n=12,849)	Mild Renal Function (n=2,774)	Moderate Renal Function (n=179)	Normal Renal Function (n=457)	Mild Renal Function (n=287)	Moderate Renal Function (n=56)
Any treatment-related AE, n (%)	522 (4)	140 (5)	15 (8)	44 (10)	38 (13)	8 (14)
AKI, n (%)	9 (<0.1)	4 (<1)	2 (1)	9 (2)	12 (4)	3 (5)
Renal impairment, n (%)	0	2 (<1)	4 (2)	0	1 (<1)	2 (4)
Hematuria, n (%)	-	-	-	6 (1)	3 (1)	1 (2)

Retrospective, Single-Center Chart Review[8]

Study Design and Demographics

Aby et al conducted a retrospective chart review of all patients who received IFN-free HCV treatment between January 1, 2014 to June 1, 2016 at the Veterans Affairs Greater Los Angeles Healthcare System. Patients were matched by age, gender, and ethnicity to a control group of non-treated patients between January 1, 2011 and January 1, 2013. Renal function results for the 2 years prior and 1 year after treatment were collected, and the primary endpoint was achievement of SVR12.

Comorbidities such as obesity, diabetes, congestive heart failure, coronary artery disease, and peripheral artery disease, and the proportion of patients who used diuretics were similar between those who achieved SVR12 and those who did not. The treatment group had significantly greater proportions of cirrhosis and obesity, whereas the control group had greater proportions of patients with hypertension, and no congestive heart failure than those in the treatment group.

Table 6. Baseline Demographics and Disease Characteristics (Aby et al)[8]

Key Demographics and Characteristics	All Patients (n=523)	SVR12 Achieved (n=485)	SVR12 Not Achieved (n=38)	*P*-value	Control Patients (n=439)	*P*-value
Age, mean (SE) years	62.7 (0.3)	63.0 (0.3)	60.5 (1.1)	0.02	63.2	0.13
Male, %	97.9	97.9	94.7	0.81	98.1	0.75
White/Black or African American, %	53.3/33.3	56.3/33.2	52.6/34.3	0.78	55.4/35.1	0.3
Cirrhosis, %	48.6	48.3	52.8	0.31	28.0	0.001
MELD score, median (IQR)	8.4 (7.5, 9.7)	N/A	N/A	N/A	7.7 (6.4, 9.2)	0.19
TN, %	77.6	77.9	73.7	0.54	N/A	N/A
HCV GT 1a/1b/2/3/4/6/multiple, %	53.2/28.1/9.2/7.6/1.1/<1/<1	53.3/28.6/8.9/6.9/1.2/<1/<1	50.7/22.2/12.6/17.1/0/0/0	0.44	55.9/22.8/11.8/6.7/1.7/0/0	0.31
Baseline CKD Stage 1/2/3/4, %	50/42/8/<1	50/42/9/<1	61/40/0/0	0.24	47.1/37.8/5.4/<1	0.56
DAA treatment						
LDV/SOF, %	38.2	37.7	44.7	0.68	N/A	N/A
SOF + RBV, %	31.4	31.8	26.3			
PrOD, %	19.9	19.6	23.7			
SIM, %	10.5	10.9	5.3			

Changes in eGFR

There was no significant difference in the changes in eGFR for those in the control group and those who achieved SVR12 (*P*=0.43; Table 7). Treatment with PrOD or LDV/SOF was associated with a significantly greater decline in eGFR in the 1-year post-treatment than the decline seen in the 1-year pre-treatment (*P*=0.005). In patients who received SOF-based treatment, those who achieved SVR12 did not have significant eGFR changes compared to those who did not achieve SVR12 (*P*=0.68).

Table 7. eGFR Changes and Comparisons in All Patients (Aby et al)[8]

eGFR Comparisons	Changes in eGFR (mean [SE], mL/min/1.73 m^2)	*P*-value
Achieved SVR12 vs SVR12 not achieved	-3.1 (0.8) vs -11.0 (2.8)	0.002
Achieved SVR12 and eGFR 1-year pre-treatment vs 1-year post-treatment	-6.2 (1.1) vs -1.8 (0.8)	0.002
SVR12 not achieved and eGFR 1-year pre-treatment vs 1-year post-treatment	-5.4 (2.8) vs -7.4 (2.2)	0.62
Control group and 2-year change in eGFR vs achieved SVR12	-2.8 (1.0) vs -3.1 (0.8)	0.43

Retrospective, Single-Center Study[9]

Study Design and Demographics

Brown et al conducted a single-center, retrospective, observational study of patients who received LDV/SOF ± RBV between October 1, 2014 and October 1, 2015 at the Henry Ford Health Hospital in Detroit, Michigan. Patients with a history of hepatic transplantation were excluded. The primary endpoint was the prevalence of AKI during treatment (≥0.3 mg/dL or ≥50% increase in SCr from baseline or ≥25% decrease in $eGFR_{MDRD}$ from baseline).

Table 8. Baseline Demographics and Disease Characteristics (Brown et al)[9]

Key Demographics and Characteristics	All Patients (N=197)
Age, mean (SD), years	60.7 (9.3)
Male, n (%)	117 (59)
Race, African American/Caucasian/ Other, n (%)	90 (45)/78 (40)/29 (15)
HCV GT, 1/2/3/unknown, n (%)	189 (95)/5 (3)/3 (2)/1 (<1)
Cirrhosis, n (%)	72 (37)
TN, n (%)	109 (55)
Treatment length, 8/12/16/24 weeks, n (%)	14 (7)/133 (67)/1 (<1)/49 (25)
CKD stage, 1/2/3/4, n (%)	119 (60)/63 (32)/14 (7)/1 (<1)

Results

Ninety-four percent of patients (n=186) achieved SVR12. Of the 11 patients who experienced treatment failure, 10 (91%) were GT 1, 8 (73%) were female, 8 (73%) had cirrhosis, 7 (64%) were TN, and 7 (64%) had CKD Stage 1, 2 (18%) had CKD Stage 2 and 2 (18%) had CKD Stage 3 renal impairment). Thirteen of the 15 patients with CKD Stage ≥3 achieved SVR12.

Thirty-eight patients (19%) experienced AKI during treatment, and an additional 4 patients (2%) had AKI after treatment. Six patients had significant decreases in eGFR (>50% of baseline eGFR reduction). The incidence of AKI was not statistically different among those with and without cirrhosis (25% vs 16%; *P*=0.124). Eighteen patients did not experience resolution of AKI by SVR12, 6 recovered at post-treatment Month 6, and 12 patients had continued AKI after post-treatment Month 6. Sixteen of the 18 patients who did not have renal recovery at Week 12 post-treatment achieved SVR12. Of those who did not achieve SVR12, one had resolution of their AKI and the other had continued AKI.

Sixty-four patients experienced eGFR reductions ≥25% from baseline, including 6 patients (9%) who had eGFR reductions of ≥50% from baseline. Thirty-five of the 64 patients had resolution of AKI. Five of the 6 patients with significant eGFR reductions improved eGFR to between <50% and >25% from baseline (1 improved to <25% of eGFR decreases). Eleven additional patients experienced eGFR reductions ≥25% from baseline post-treatment.

Multivariate logistic regression revealed that CKD Stage ≥3 (OR: 8.19; 95% CI: 1.8, 37.3; P=0.007), males (OR: 3.32; 95% CI: 1.19, 9.26; *P*=0.022), and patient age (OR: 1.08; 95% CI: 1.02, 1.15; *P*=0.015) were statistically significantly associated with AKI.

Italian Retrospective Cohort Study[10]

Study Design and Demographics

Strazzulla et al conducted a retrospective study to evaluate the changes in $eGFR_{CKD\text{-}EPI}$ (baseline vs EOT, baseline vs SVR12, and EOT vs SVR12) among 149 patients who received DAAs from January 31, 2014 and October 31, 2016 at a hospital in Catanzaro, Italy. Patients treated with LDV/SOF were included in a subgroup analysis of serum NGAL, a kidney biomarker, to assess AKI (n=18). One hundred forty-nine patients received 162 treatments of DAAs (10 received 2 different DAA regimens and 1 received 4 different DAA regimens), and eGFR changes were evaluated in 102 treatment courses (in 99 patients). The gender distribution, mean age, prevalence of cirrhosis, mean FIB-4 score, and mean eGFR values were similar at baseline among the overall population, eGFR study population, and NGAL study population (*P*<0.05; Table 9).

Table 9. Baseline Demographics and Disease Characteristics (Strazzulla et al)[10]

Key Demographics and Characteristics	Overall (N=149)	eGFR Study Population (n=99)	NGAL Study Population (n=18)
Age, ≥65 years, n (%)	86 (58)	62 (63)	12 (67)
Male, n (%)	84 (56)	54 (55)	11 (61)
Cirrhosis, n (%)	77 (48)	51 (52)	9 (50)
Child-Pugh-Turcotte, A/B/C, n (%)	147 (99)/2 (1)/0	99 (100)/0/0	18 (100)/0/0
GT 1a/1b/2/3/4, n (%)	6 (4)/124 (76)/21 (13)/5 (3)/6 (4)	3 (3)/72 (73)/17 (17)/2 (2)/5 (4)	1 (6)/17 (94)/0/0/0
IFN-experienced, n (%)	81 (54)	56 (57)	12 (67)
Comorbidities, DM/HTN, n (%)	34 (23)/68 (46)	24 (24)/54 (55)	5 (28)/9 (50)
Concomitant NSAID use, n (%)	9 (6)	7 (7)	1 (6)
CKD stage			
Stage 1, n (%)	84 (52)	54 (55)	9 (50)
Stage 2, n (%)	62 (38)	37 (37)	7 (39)
Stage 3a/3b, n (%)	9 (5)/6 (4)	4 (4)/4 (4)	2 (11)/0
Stage 4, n (%)	0	0	0
Stage 5, n (%)	1 (1)	0	0
Hemodialysis, n (%)	2 (1)	0	0
SCr, mean (SD), mg/dL	0.9 (0.8)	0.8 (0.2)	0.8 (0.2)
eGFR, mean (SD), mL/min	86 (19)	86 (17)	83 (18)
Treatment duration, 12/24/48 weeks, n (%)	81 (50)/64 (40)/17 (10)	61 (60)/41 (40)/0	6 (33)/12 (67)/0

Table 10. DAA Regimen by Study Population (Strazzulla et al)[10]

DAA Regimen	Overall (N=149)	eGFR Study Population (n=99)	NGAL Study Population (n=18)
+RBV, n (%)	94 (58)	55 (54)	6 (33)
LDV/SOF, n (%)	57 (35)	38 (37)	18 (100)
SOF + SIM, n (%)	37 (23)	31 (30)	0
SOF + DCV, n (%)	27 (17)	16 (16)	0
SOF, n (%)	13 (8)	12 (12)	0
SOF + SIM + DCV, n (%)	1 (1)	0	0
IFN + TPV, n (%)	16 (10)	0	0
PrOD + dasabuvir, n (%)	4 (2)	3 (3)	0
IFN + BOC, n (%)	4 (2)	0	0
SIM + DCV, n (%)	2 (1)	2 (2)	0
IFN + SIM, n (%)	1 (1)	0	0

Efficacy

SVR12 was achieved by 76% of patients (123/162; no data in 18 patients and 8 were lost to follow-up) in the overall population, 95% of patients (97/102) in the eGFR population, and 100% of patients in the NGAL population.

eGFR Results

The decrease in eGFR was significantly different from baseline to SVR12 in the eGFR study population (86.22 mL/min/1.73 m2 vs 84.3 mL/min/1.73 m^2, respectively; *P*=0.049). Differences in eGFR from baseline to EOT (*P*=0.219), and EOT to SVR12 (*P*=0.415) were not statistically significant. The addition of RBV was associated with a significant decrease in eGFR from baseline to SVR12 (87.12 22 mL/min/1.73 m^2 vs 84.4 22 mL/min/1.73 m^2, respectively; *P*=0.045); conversely, similar decreases in eGFR from baseline were observed when RBV was not added to DAAs (85.17 22 mL/min/1.73 m^2 vs 83.95 22 mL/min/1.73 m^2, respectively; *P*=0.822). Patients with CKD Stage 1 renal impairment had significant reductions in

eGFR from baseline (97.99 mL/min/1.73 m^2) to EOT (94.46 mL/min/1.73 m^2; *P*<0.001) and from EOT to SVR12 (93.83 mL/min/1.73 m^2; *P*<0.001).

Baseline HCV RNA levels, DAA regimen, cirrhosis presence, age, and BMI rankings did not affect eGFR levels significantly. No associations were observed between the change in eGFR from baseline to EOT and age, gender, addition of RBV, or the presence of cirrhosis (*P*<0.05).

NGAL Results

Mean NGAL values were significantly increased from baseline to SVR12 in the NGAL study population (121.89 ng/mL vs 204.13 ng/mL; *P*=0.014). Patients without cirrhosis had significantly higher NGAL levels at SVR12 than at baseline (187.85 ng/mL vs 85.33 ng/mL, respectively; *P*=0.021).

Within the NGAL study population, eGFR levels were not significantly different from baseline to SVR12 (*P*=0.801), from baseline to EOT (*P*=0.524), or EOT to SVR12 (*P*=0.648). Seven patients in the NGAL study population had NGAL levels above normal range, which was numerically higher than 2 patients with elevated NGAL levels at baseline (*P*=0.054; χ^2=3704). Compared with a negligible eGFR decline observed in the whole cohort, a significant NGAL increase was observed after DAA treatment in a small subgroup who received LDV/SOF. The study authors suggested that this could have been a reflection of tubular damage or inflammation during DAA treatment rather than glomerular injury.

Retrospective Cohort Study[11]

Study Design and Demographics

Rosenblatt et al retrospectively analyzed patients with pre-existing moderate renal impairment (eGFR <60 mL/min/1.73 m^2), to evaluate whether this patient population were at a higher risk of worsened kidney disease after treatment with LDV/SOF. Assessments of SCr and $eGFR_{MDRD}$ were conducted at baseline, Week 4 of treatment, EOT, post-treatment Week 4, and at SVR12.

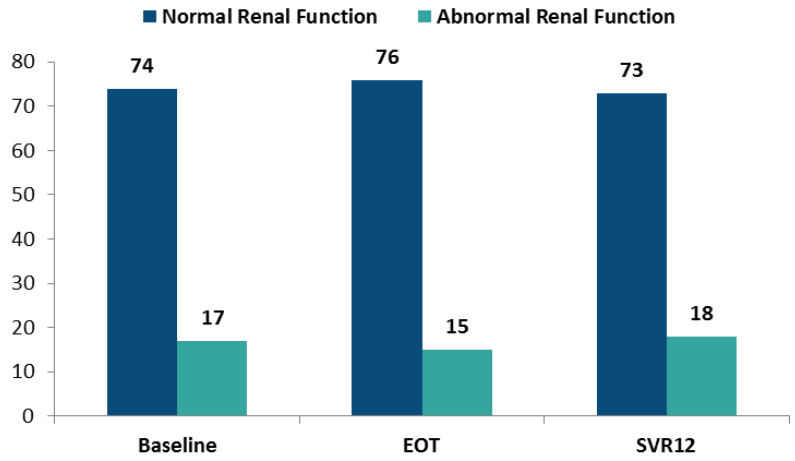
Table 11. Baseline Demographics and Disease Characteristics (Rosenblatt et al)[11]

Key Demographics and Characteristics	Normal eGFR (n=74)	Abnormal eGFR (n=17)	*P*-value
Age, mean, years	58	62	0.2
Male, n (%)	32 (43)	9 (53)	0.47
TN, n (%)	52 (70)	10 (59)	0.36
Advanced fibrosis, n (%)	20 (27)	7 (41)	0.24
HCV RNA, mean, IU/mL	2,948,394	3,347,602	0.67
+RBV, n (%)	2 (3)	2 (12)	0.1
Treatment length, 8/12/24 weeks, n (%)	13 (18)/56 (76)/5 (7)	2 (12)/12 (71)/3 (18)	0.33

Results

Similar rates of SVR12 were achieved by those with abnormal and normal baseline renal function: 94% (16/17) vs 97% (72/74; *P*=0.5). Most of the patients (61/74) who initially had normal renal function at baseline maintained normal renal function at SVR12. Five of the 17 patients who initially had abnormal renal function at baseline improved their renal function at SVR12, and 11 patients continued to have abnormal renal function at SVR12 (Figure 2; values for 1 patient were not reported).

Figure 2. Patients with Normal and Abnormal Renal Function Throughout Study (Rosenblatt et al)[11]



Patients with abnormal baseline renal function were associated with continued abnormal renal function after controlling for age, length of treatment, and advanced fibrosis (Table 12).

Table 12. Univariate and Multivariate Analyses of Factors associated with Worsened Renal Function (Rosenblatt et al)[11]

Baseline Factors	Univariate Analysis		Multivariate Analysis	
	OR	*P*-value	OR	*P*-value
Baseline abnormal renal function (<60 mL/min/1.73 m^2)	4.72	0.029	4.23	0.04
Treatment duration	1.68	0.43	1.30	0.74
Advanced fibrosis	2.20	0.22	1.97	0.34
Age	-	-	1.08	0.10

Systematic Reviews

Systematic Review of SOF-Induced Nephrotoxicity[12]

Study Design

Dashti-Khavidaki et al conducted a systematic review to summarize data on the epidemiology, type, and potential risk factors for nephrotoxicity due to SOF-based treatment.

Incidence of SOF-Induced AKI

Based upon the available data, the study authors estimated that SOF-induced AKI occurred in 1% to 15% of patients. The reported rate of SOF-induced AKI was higher among liver transplant recipients at 37.5% to 46.7%. No observed differences in SOF-induced AKI were observed in patients with moderate renal impairment in comparison to patients with severe renal impairment. AKI onset occurred at a median 9 (range: 4-22) weeks after SOF initiation, and impairment was reversible after SOF was discontinued.

Type of SOF-Induced AKI

AIN was observed in the histologic samples of 4 patients who developed AKI after SOF treatment (Table 13).

Table 13. Histologic Results of Patients' Kidney Biopsies with SOF-Induced AKI[12]

Gender	Age	SOF-Based Treatment	Time from SOF Initiation to AKI	Histologic Findings
Female	62 years	LDV/SOF	8 weeks	AIN, diabetic nephropathy
Female	56 years	LDV/SOF	8 weeks	AIN, acute tubular necrosis[a]
Male	66 years	SOF + DCV	22 weeks	AIN, background of mesangioproliferative immunoglobulin A nephropathy
Male	Not specified	SOF + DCV	16 weeks	AIN

[a]This patient was HIV-infected, and was treated with efavirenz, tenofovir disoproxil fumarate, and emtricitabine. Eight weeks after LDV/SOF was added, SCr increased from 0.9-1 mg/dL at baseline to 10 mg/dL. LDV/SOF and tenofovir were discontinued, and a prednisolone taper was initiated. Six weeks afterwards, her SCr decreased to 1.3 mg/dL. The study authors attributed the AIN may have been due to LDV/SOF and not due to increased tenofovir levels.

Risk Factors for SOF-Induced AKI

Potential risk factors for SOF-induced AKI identified from studies included the following: concomitant nephrotoxic agent treatment (calcineurin inhibitors in organ transplant recipients or NSAIDs), older age, cirrhosis, diabetes, a baseline eGFR ≤45 mL/min/1.73 m^2, those with CKD Stage 1 or 2 and cirrhosis, those with CKD Stage 3 with diabetes, baseline MELD scores, ascites presence, and low baseline albumin levels.

SOF Drug Interactions

Some guidelines recommend that tenofovir and LDV/SOF should not be used concomitantly in patients with eGFR <60 mL/min/1.73 m^2 as it is postulated that LDV can increase tenofovir exposure and the risk of adverse events. A pharmacokinetic study also showed that tenofovir's exposure was increased by 40% to 98% by LDV. One study did not confirm this relationship; however, another study of HCV/HIV-co-infected patients treated with LDV/SOF and tenofovir 4 patients reported SCr increases of >0.4 mg/dL. Overall, the study authors suggest that concomitant use of tenofovir, which can be tubulotoxic, with drugs that have a high-risk of AIN (eg, SOF), nephrotoxicity and SCr increases may occur.

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Abbreviations

ACEI=angiotensin converting enzyme inhibitor
AE=adverse event
AIN=acute interstitial nephritis
AKI=acute kidney injury
ARB=angiotensin receptor blocker
BOC=boceprevir
CKD=chronic kidney disease
DAA=direct-acting antiviral
DCV=daclatasvir
DM=diabetes mellitus
$eGFR_{CG}$=estimated glomerular function by Cockroft-Gault equation
$eGFR_{CKD-EPI}$=estimated glomerular function by the CKD Epidemiology Collaboration equation
$eGFR_{MDRDI}$=estimated glomerular function by Modification of Diet in Renal Disease study equation
ESRD=end-stage renal disease
GLMM=generalized linear mixed-effect model
GT=genotype
HTN=hypertension
IFN=interferon
IQR=interquartile range
LDV=ledipasvir
MELD=model for end-stage liver disease
N/A=not applicable or not available
NGAL=neutrophil gelatinase associated lipocalin
NSAID=non-steroidal anti-inflammatory drug
PegIFN=pegylated interferon
PrOD=paritaprevir + ritonavir + ombitasvir + dasabuvir
RBV=ribavirin
SD=standard deviation
SIM=simeprevir
SOF=sofosbuvir
SVR12=sustained virologic response 12 weeks post-treatment
SVR24= sustained virologic response 12 weeks post-treatment
TE=treatment-experienced
TN=treatment-naïve
TPV=telaprevir
VEL=velpatasvir
VOX=voxilaprevir

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