Hepatic Decompensation and SAEs in HCV infected Patients on Sofosbuvir- and/or Simeprevir-based Therapies

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Abstract

Background: New therapies for hepatitis C virus (HCV) were well-tolerated in registration trials, but results in practice can differ. We characterized patients experiencing hepatic decompensation and serious adverse events (SAEs) in a real-world setting and to identify potential risk factors.

Methods: Records of patients on sofosbuvir (SOF) and/or simeprevir (SMV) were reviewed. Cases had at least one of the following: hepatic decompensation, indicated by new or increased jaundice, ascites, encephalopathy, variceal bleeding, sepsis, or another SAE. The study group was comprised of patients who had not undergone liver transplantation (LT) (Cohort 1), and patients who had undergone LT (Cohort 2). The incidence of decompensation/SAE was calculated for each cohort by Kaplan-Meier analysis. In addition, a matched Case-Control study was performed to identify risk factors for decompensation/SAE for non-LT patients. For Cohort 1, five Controls were selected for each Case based on treatment regimen and duration. For Cohort 2, cases and controls were not matched. Within Cohort 1, Cases and Controls were compared using matched conditional exact analysis, whereas Cases and Controls for Cohort 2 were compared using exact logistic regression analysis.

Results: A total of 541 patients met the inclusion criteria: 499 in Cohort 1 (non-LT) and 42 in Cohort 2 (LT). There were 16 non-LT Cases and 13 LT cases. The incidence of decompensation/SAE was 4.5% in Cohort 1 (non-LT) and 31% in Cohort 2 (LT). In Cohort 1 (non-LT), 86 patients were on PEG/RBV-free regimens; three of them decompensated/experienced an SAE. Treatment was discontinued in 7/16 (44%) of non-LT Cases and in 3/13 (23%) of LT Cases. Liver decompensation/SAE led to treatment discontinuation in 1.4% (7/499) of Cohort 1 and in 7.1% (3/42) of Cohort 2 (similar to results in registration trials). In Cohort 1, risk factors for SAE/decompensation included low baseline albumin and high total bilirubin.

Conclusions: 4.5% of patients in Cohort 1 and 31% of patients in Cohort 2 experienced liver decompensation or an SAE during treatment or within one month of ending treatment. The untoward events in Cohort 1 were likely to be treatment related because the *Cases had not had similar events for at least the 12 month period prior to starting treatment*. Low hepatic reserve may have contributed to risk of decompensation/SAE in Cohort 1, while low hemoglobin and eGFR may have contributed to the composite outcome in Cohort 2. The underlying mechanisms leading to life-threatening adverse events or decompensation from SOF- and/or SMV-containing regimens need to be investigated further.

Aims

- To determine the incidence and nature of SAEs and/or hepatic decompensation events in HCV patients on SOF- and/or SMV-containing regimens
- To identify risk factors associated with these untoward effects of treatment

Methods

We identified patients who experienced an SAE and/or hepatic decompensation during or up to one month following the end of treatment (EOT). For data analysis, the study group was comprised of patients who had not undergone LT (Cohort 1, which included 499 patients), and patients who had undergone LT (Cohort 2, which included 42 patients). Inclusion criteria included age ≥ 18 years, initiation of HCV treatment at Mount Sinai Hospital, December 2013-June 2014, and receiving at least one dose of a SOF- or SMV-containing regimen. HIV-positive patients were excluded. Data were collected on demographics, medical history including comorbid conditions, stage of liver disease, baseline and on- treatment laboratory values, description of the decompensation/SAE, and SVR. Each episode of decompensation/SAE could involve multiple complications. Cirrhosis was defined by any of the following: liver biopsy with stage 4 fibrosis; liver biopsy with stage 3 fibrosis plus any one of the following: platelets <140,000 cells/mL, presence of esophageal varices on upper endoscopy, imaging study with evidence of cirrhosis and/or portal hypertension, history of ascites. In the absence of a liver biopsy, any two of the following: platelets <140,000 cells/mL, presence of varices on upper endoscopy, imaging with evidence of cirrhosis and/or portal hypertension, history of ascites. The study had IRB approval (GCO # 10-0032).

Case Definition: New-onset hepatic decompensation, indicated by new or increased jaundice, ascites, encephalopathy, variceal bleeding, sepsis, or another SAE (according to the FDA definition) while on treatment or during the first month EOT. *Medical records were reviewed to verify the absence of hepatic decompensation events for the 12 months prior to study entry (for Cohort 1)*. To assess causality, the healthcare provider for each Case assigned a score for decompensation/SAE events based on a 5 point scale (for Cohort 1).

Controls: Controls received the same treatment regimen as Cases and treatment duration was at least as long as the corresponding Case. In Cohort 1 (non-LT) five Controls were randomly selected for each Case. In Cohort 2 (LT), we did not perform matched analysis due to small sample size.

Statistical analysis: Data of Cohorts 1 and 2 were analyzed separately. A nested matched Case-Control study was performed with Cohort 1, while an unmatched Case-Control study was performed with Cohort 2. For Cohort 1, we used conditional exact logistic regression to identify factors associated with hepatic decompensation and SAEs, while exact logistic regression analysis was used for Cohort 2. All untoward events were included in the analysis of risk factors, but only the time to the first event was included in the calculation of incidence. Kaplan-Meier curves were used to determine the cumulative-incidence of SAE/decompensation. A p-value < 0.05 was considered significant.

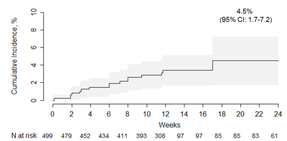
Cohort 1: non-LT

Baseline Characteristics, Univariable and Multivariable Analyses

	Categorical: n Case n=16	Continuous: median (IQR) Controls n=80	p-value	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Demographics and Anthropometrics									
Age, yr	59 (54-67)	59 (54-63)	0.55	1.02	0.96-1.09	0.65	.	.	.
Gender, female	5 (31%)	27 (34%)	.	0.94	0.22-3.48	1.00	.	.	.
Race, Black	4 (25%)	9 (11%)	.	2.71	0.51-16.06	0.28	.	.	.
Ethnicity, Hispanic	2 (13%)	17 (21%)	.	0.40	0.04-2.09	0.41	.	.	.
Weight, lb	182 (147-200)	180 (155-205)	0.17	0.99	0.98-1.01	0.52	.	.	.
BMI, kg/m^2	27.9 (24.6-31.4)	27.8 (25.4-30.5)	0.59	0.97	0.85-1.11	0.73	.	.	.
Comorbidities									
HCC	3 (19%)	6 (8%)	.	2.54	0.41-14.54	0.35	.	.	.
Diabetes	6 (38%)	15 (19%)	.	2.45	0.66-9.05	0.20	.	.	.
Hypertension	6 (38%)	36 (45%)	.	0.74	0.21-2.41	0.77	.	.	.
Depression	0 (0%)	21 (26%)	.	0.14	<0.1-0.67	0.03	.	.	.
Liver Disease Severity									.
Cirrhosis	12 (75%)	46 (58%)	.	2.96	0.63-17.48	0.21	.	.	.
Fib-4	9.36 (2.79-12.21)	4.90 (1.78-8.58)	0.27	1.07	0.98-1.17	0.15	.	.	.
Fib-4 ≥3.25	11 (69%)	47 (59%)	.	1.74	0.44-7.79	0.54	.	.	.
MELD	14 (10-17)	8 (7-10.25)	<0.01	1.74	1.20-2.52	<0.01	.	.	.
Treatment Naïve	7 (44%)	41 (51%)	.	0.74	0.21-2.43	0.78			
Genotype									
1	11(69%)	49 (61%)	.	Ref	Ref	Ref			
2	1 (6%)	8 (10%)	.	0.42	0.01-8.02	0.96			
3	3 (19%)	18 (23%)	.	0.72	0.12-3.26	0.90			
4	1 (9%)	5 (6%)	.	0.90	0.02-9.63	1.00			
Labs									
Hemoglobin, g/dL	12.6 (11.3-13.8)	14.2 (12.8-15.4)	0.04	0.64	0.47-0.90	<0.01	.	.	.
Platelets, x103/µL	81 (59-148)	140 (81-189)	0.27	0.99	0.99-1.01	0.54	.	.	.
HCV viral load, log10 (IU/mL)	5.93 (4.67-6.20)	5.98 (5.29-6.45)	0.23	0.71	0.40-1.26	0.24	.	.	.
Serum creatinine, mg/dL	0.92 (0.73-1.07)	0.92 (0.76-1.01)	0.83	1.36	0.18-8.62	0.71	.	.	.
eGFR, mL/min /1.73 m^2	96 (79-99)	88 (76-98)	0.55	1.01	0.98-1.04	0.57	.	.	.
Albumin, g/dL	3.0 (2.2-3.8)	3.9 (3.5-4.3)	<0.01	0.11	0.03-0.37	<0.01	0.12	0.01-0.61	0.01
ALT, U/L	51 (43-84)	78 (43-106)	0.11	0.99	0.98-1.00	0.13	.	.	.
AST, U/L	82 (49-108)	73 (41-106)	0.67	0.99	0.99-1.01	0.72	.	.	.
INR	1.4 (1.1-1.7)	1.1 (1.0-1.2)	<0.01	1.63	1.17-2.28	<0.01	.	.	.
Total bilirubin, mg/dL	1.8 (1.2-2.7)	0.8 (0.5-1.2)	<0.01	5.67	1.98-16.28	<0.01	4.31	1.32-19.60	0.01
Alpha fetoprotein, ng/mL	9.0 (5.0-18.6)	9.3 (4.7-24.8)	0.10	0.99	0.95-1.00	0.30	.	.	.

Incidence of Hepatic Decompensation/SAE

Cohort 1



- **The cumulative incidence of decompensation or SAE in the non-LT cohort was 4.5% (95% CI = 1.7 - 7.2).**
- **An average of 6.3 weeks passed until 1st episode of decompensation/SAE**
- **There was an average of 1.9 episodes per Case**

Hepatic Decompensation/SAE

	Total n=16	SOF/RBV n=11	SOF/PEG/RBV n=2	SMV/SOF n=3
Treatment Discontinued	7(44%)	4	1	2
Decompensation**	**11(69%)**	**9**	**0**	**2**
Jaundice	7 (44%)	5	0	2
Encephalopathy	2 (13%)	2	0	0
Ascites	4 (25%)	4	0	0
Sepsis	6 (38%)	5	0	1
Variceal Bleed	2 (13%)	2	0	0
SAE**	**14(87%)**	**10**	**2**	**2**
Hospitalization	11 (69%)	10	0	1
Anemia requiring transfusion	4 (25%)	4	0	0
LFT elevation	2 (13%)	0	0	2
Death	2 (13%)	2	0	0
Other*	6 (38%)	4	2	0

*** hyperkalemia, SVT, AKI, intraocular bleeding, thrombocytopenia, gout flare, DVT, hepatic hydrothorax, dehydration, *C. diff* colitis**

**** An episode could have more than one complication**

Cases with Decompensation/SAE Description and Overall Outcome

Case	Rx	Genotype	Age	Sex	Cirrhosis	Baseline Platelets	Baseline Albumin	Baseline Total bili	Baseline ALT	Baseline MELD	1st Event Wk	First Episode	Later Episodes	Causality Score[1]	Overall Outcome	SVR 12 (Y/N)
1	SOF/RBV 12 wk	2	78	F	Yes	81	2.0	2.3	84	*	2.9	Hospitalized for variceal bleeding, treatment discontinued	None	2	Treatment discontinued at the time of hospitalization for variceal bleed, sent to hospice/palliative care, died	N/A
2	SOF/RBV 12 wk	4	79	M	Yes	56	3.1	1.9	43	10	11.7	Hospitalized for SBP	Hospitalized for SBP and jaundice; hospitalized for worsening ascites	2	Hospitalized 3 times; SBP and ascites resolved with medical management, completed treatment, relapsed 4 weeks post-EOT	N
3	SOF/RBV 24 wk[b]	1b	55	M	Yes	61	2.4	3.5	42	14	3.9	Hyperkalemia**	Hospitalized for hepatic hydrothorax, UTI, anemia requiring transfusion	1	All issues resolved/improved with medical management; thoracentesis done for hepatic hydrothorax, fluid status controlled with diuretics; completed treatment, relapsed 18 weeks post-EOT	N/A
4	SOF/RBV 24 wk	1a	56	M	Yes	54	2.2	2.6	84	17	9.4	Hospitalized, Klebsiella bacteremia	None	2	Bacteremia resolved after antibiotic course, completed treatment, relapsed 4 weeks post-EOT	N
5	SOF/RBV 24 wk	3	57	M	Yes	69	1.7	1.1	44	15	8.0	Ascites	Hospitalized for SBP and anemia requiring transfusion; Later hospitalized for dehydration, *C. diff* colitis	1	Ascites resolved after increasing dose of diuretics, *C.diff* resolved with antibiotics; completed treatment, undetectable viral load at EOT	Lost to follow-up
6	SOF/RBV 24 wk	3	60	F	Yes	56	2.2	2.8	49	14	2.0	Hyperbilirubinemia, ascites, treatment discontinued	None	4	Ascites improved after LVP and increased dose of diuretics; total bilirubin improved to baseline after discontinuing treatment; viral load detectable at time of treatment discontinuation	N
7	SOF/RBV 24 wk	1a	61	M	Yes	154	3.2	1.5	31	13	3.0	Hospitalized for EVB, treatment discontinued	None	1	Variceal banding done with no blood transfusion; had recurrent EVB 3 months later requiring further banding; viral load detectable at time of treatment discontinuation	N
8	SOF/RBV 24 wk	1b	61	M	Yes	60	3.2	3.8	73	17	1.9	Hyperbilirubinemia	Hospitalized, PSE	3	Total bilirubin improved to baseline after RBV dose reduction, PSE improved with medications, completed treatment	Y
9	SOF/RBV 24 wk	1a	67	M	No	146	4.5	0.7	31	10	8.0	Hospitalized, anemia requiring transfusion, gout flare	Anemia requiring transfusion	4	Hemoglobin improved after transfusion, gout flare resolved with steroids; completed treatment	Y
10	SOF/RBV 24 wk	1b	67	M	Yes	175	2.9	1.6	22	16	6.0	SVT,AKI, anemia requiring transfusion	Hospitalized, anemia requiring transfusion, hepatic hydrothorax	2	SVT and AKI resolved, hemoglobin improved after transfusion, hydrothorax improved after thoracentesis; treatment completed, relapsed 18 weeks post-EOT	N
11	SOF/RBV 24 wk	3	69	F	Yes	81	2.3	2.1	48	17	0.1	Hospitalized, PSE, UTI	Hospitalized, PSE, jaundice, worsening liver function, death	1	Progressive hepatocellular carcinoma; worsening liver function, PSE, hypotension, AKI, death; viral load undetectable prior to stopping treatment at week 11	N/A
12	SOF/PEG/RBV 12 wk[b]	1a	40	M	No	455	4.4	0.9	156	*	17.0	Deep venous thrombosis, treatment discontinued	None	2	Treated with anticoagulation	Y
13	SOF/PEG/RBV 12 wk	1b	44	F	Yes	99	3.7	1.1	128	*	7.1	Intraocular bleeding, thrombocytopenia, PEG discontinued	None	3	Completed 24 weeks of SOF/RBV	Y
14	SMV/SOF 12 wk[c]	1a	47	F	No	292	3.9	1.5	63	8	11.6	LFT elevation, hyperbilirubinemia with biopsy proven AIH, treatment discontinued	Hospitalized for urosepsis	3	AIH flare resolved after treatment	Y
15	SMV/SOF 12 wk	1b	52	M	No	135	4.5	1.2	53	8	6.0	10-fold increase in ALT, 5-fold increase in AST with positive autoimmune markers	None	3	Transaminase levels normalized, treatment completed	Y
16	SMV/SOF 12 wk	1a	58	M	Yes	55	1.6	4.9	93	19	1.9	Hyperbilirubinemia, treatment discontinued	Died 4 months after treatment discontinued***	4	Treatment discontinued after 1st episode; Died from multiorgan failure, septic shock after presenting with a syncopal episode	N/A

[a]SOF/RBV – Sofosbuvir/Ribavirin, [b]SOF/PEG/RBV – Sofosbuvir/PEG-interferon/Ribavirin, [c]SMV/SOF – Simeprevir/Sofosbuvir

MELD – Model for End-Stage Liver Disease, SBP - spontaneous bacterial peritonitis, SVR – sustained virological response, UTI - urinary tract infection, EOT – end of treatment, LVP – large volume paracentesis, EVB – esophageal variceal bleed, PSE – portosystemic encephalopathy, SVT - supraventricular tachycardia, AKI - acute kidney injury, LFT - liver function test, AIH – autoimmune hepatitis, ALT – Alanine aminotransferase, AST – aspartate aminotransferase

* There was no baseline INR, so MELD could not be calculated

** Pt had normal baseline renal function with GFR > 60

***Death occurred beyond the definition of a Case and was therefore not counted in analysis as an event

[1]Causality Score Scale: 0- Not treatment related; 1- Possibly treatment related; 2 - Probably treatment related; 3 - Likely treatment related; 4 - Certainly treatment related

Cohort 2: LT

Baseline Characteristics and Univariable Analysis

	Categorical: n Cases n=13	Continuous: median (IQR) Controls n=29	p-value	Unadjusted OR	95% CI	p-value
Demographics and Anthropometrics						
Age, yr	64 (56-68)	60 (57-64)	0.97	1.00	0.92 – 1.09	0.97
Gender, Female	6 (46%)	8 (28%)	0.15	2.13	0.47 – 9.72	0.40
Race, Black	1 (7%)	3 (10%)	1.00	0.73	0.01 – 9.98	1.00
Ethnicity, Hispanic	1 (7%)	8 (28%)	0.23	0.22	0.01 – 2.07	0.30
Weight, lbs	155 (122-168)	170 (147-193)	0.04	0.98	0.95 – 1.00	0.06
BMI, kg/m^2	25.6 (21.6-27.8)	26.7 (24.6-29.0)	0.12	0.87	0.73 – 1.04	0.13
Years since LT	4.98 (1.7 – 7.5)	5.6 (2.7 – 8.8)	0.52	0.96	0.83 – 1.10	0.52
Comorbidities						
HCC	5 (38%)	11 (38%)	1.00	1.02	0.21 – 4.78	1.00
Diabetes	6 (46%)	15 (52%)	1.00	0.80	0.17 – 3.58	1.00
Hypertension	9 (69%)	18 (62%)	0.74	1.40	0.29 – 7.76	0.91
Depression	1 (8%)	4 (14%)	1.00	0.54	0.01 – 6.05	1.00
Liver Disease Severity						
Cirrhosis	3 (23%)	5 (17%)	0.69	1.42	0.19 – 9.49	0.96
Fib-4	6.57 (3.12-8.94)	4.49(2.78-6.71)	0.24	1.07	0.95 – 1.20	0.29
Fib-4 ≥3.25	9 (69%)	19(65%)	1.00	1.17	0.25 – 6.70	1.00
Treatment Naïve	3 (23%)	6 (21%)	1.00	1.14	0.15 – 6.77	1.00
Genotype						
1	8(62%)	23 (79%)	0.27	REF	REF	REF
2	2 (15%)	1 (3%)	0.22	6.25	0.26-477.66	0.39
3	2 (15%)	3 (10%)	0.64	1.90	0.13 – 18.36	0.86
4	1 (8%)	1 (3%)	0.53	2.75	0.03 – 228.51	0.95
Labs						
Hemoglobin, g/dL	11.3 (9.6-12.4)	12.9 (12.2-14.5)	0.01	0.61	0.40 – 0.88	<0.01
Platelets, x103 /µL	113 (85-138)	121 (81-150)	0.21	0.99	0.98 – 1.00	0.26
HCV viral load, log10(IU/mL)	6.59 (6.07-6.70)	6.53 (6.32-6.76)	0.81	0.90	0.38 – 2.44	0.82
Serum creatinine, mg/dL	1.60 (1.33-1.86)	1.23 (1.04-1.60)	0.06	2.27	0.88 – 8.82	0.09
eGFR, mL/min /1.73 m^2	42 (32-49)	56(44-70)	0.01	0.95	0.90 – 0.99	0.01
Albumin, g/dL	3.6 (2.9-3.9)	3.8 (3.6-4.1)	0.23	0.45	0.13 – 1.32	0.15
ALT, U/L	43 (33-72)	65 (42-89)	0.15	0.99	0.97 – 1.00	0.19
AST, U/L	61 (53-77)	64 (41-93)	0.95	1.00	0.99 – 1.00	0.54
INR	1.0 (0.9-1.3)	1.0 (1.0-1.1)	0.85[b]	1.27	1.12 – 1.14	0.22
Total bilirubin, mg/dL	0.8 (0.6-2.2)	0.7 (0.5-1.0)	0.10	2.43	1.17 – 8.65	<0.01
Alpha fetoprotein, ng/mL	5.0 (3.5-12.1)	5.0 (3.0-8.2)	0.40	0.25	0.99 – 1.11	0.15

Hepatic Decompensation/SAE

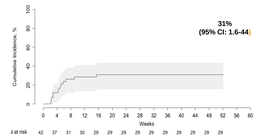
	SOF/RBV N=12	SOF/PEG/RBV N=1
Treatment Discontinued	3	0
Decompensation**	**7**	**0**
Jaundice	3	0
Encephalopathy	2	0
Ascites	1	0
Sepsis	4	0
SAE**	**12**	**1**
Hospitalization	8	0
Anemia requiring transfusion	7	1
LFT elevation	0	0
Death*	2	0
Other**	3	0

- **2 patients died; one from complications of intracranial hemorrhage, the other was transitioned to palliative care 1 month after starting treatment**
- **** failure to thrive, ocular pain, blurry vision, anemia w/o transfusion (treatment D/C), hyperkalemia, partial small bowel obstruction**

***** An episode could have more than one complication**

Incidence of Hepatic Decompensation/SAE

Cohort 2



- **The cumulative incidence for decompensation or SAE in the LT cohort was 31% (95% CI = 1.6 - 44).**
- **An average of 4.9 weeks passed until 1st episode of decompensation/SAE**
- **There was an average of 2.5 episodes per Case**

Summary and Conclusions

Cohort 1 (non-LT)

- **4.5% of patients experienced liver decompensation or an SAE during treatment or within one month after EOT.**
- **The untoward events were likely to be treatment related because the *Cases had not had similar events for at least the 12 month period prior to starting treatment.***
- ***Three Cases died unexpectedly with no underlying conditions considered to be life-threatening. One patient was Child Pugh Class C who was prescribed SMV/SOF. The overall mortality was 0.6%***
- **Of the 13 surviving patients, four relapsed after EOT, one was viral load undetectable at EOT, two were viral load detectable at the time of treatment discontinuation, and six achieved SVR 12.**
- **Liver decompensation or an SAE led to treatment discontinuation in 1.4% (7/499).**
- **Risk factors for decompensation/SAE included low baseline albumin and high total bilirubin. Interestingly, fibrosis stage was not a risk factor which may have been related to overall high percentage with more advanced liver disease or cirrhosis.**
- **The 4.5% incidence of decompensation/SAE suggests that a subgroup may exist who could benefit from more intensive monitoring or some type of intervention.**

Cohort 2 (LT)

- **Thirty one percent of patients experienced liver decompensation or an SAE during treatment or within one month of ending treatment, with anemia requiring transfusion the most common event.**
- **Liver decompensation or an SAE led to treatment discontinuation in 7.1% (3/42).**
- **Lower baseline hemoglobin and eGFR, and high baseline total bilirubin were possible risk factors for hepatic decompensation/SAE**

Conclusion

- **Rather than the stage of fibrosis, low hepatic reserve may have increased risk in the non-LT patients.**
- **Based on past and current data, SMV should not be used in Child Pugh Class C patients**
- **The underlying mechanisms leading to life-threatening adverse events or decompensation from SOF- and/or SMV-containing regimens need to be investigated further.**