Acute Kidney Injury in Patients Undergoing Chronic Hepatitis C Virus Treatment With Ledipasvir/Sofosbuvir

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Acute Kidney Injury in Patients Undergoing Chronic Hepatitis C Virus Treatment With Ledipasvir/Sofosbuvir

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Ledipasvir-sofosbuvir, a once-a-day, oral combination pill, was approved in 2014 for the treatment of chronic hepatitis C infection. Initial trials did not comment on nephrotoxicity; however, recent data suggest a risk of acute kidney injury (AKI) with the use of the medication. We assessed the rates of AKI in patients undergoing ledipasvir-sofosbuvir in a large, urban tertiary care center. This single-center retrospective observation study included all patients undergoing therapy from October 1, 2014, to October 1, 2015. Rates of AKI, defined by more than a 0.3 mg/dL increase in serum creatinine level, were calculated. Patients were followed 12 weeks after therapy to assess for sustained viral response as well as to assess for improvement of AKI after completion of therapy, defined by less than 0.2 mg/dL above baseline serum creatinine. In total, 197 patients were included in the final analysis who had completed ledipasvir-sofosbuvir therapy and completed laboratory values. Among the patients treated, 38 (19%) had AKI during therapy. An additional 4 (2%) had AKI at the end of therapy. Of the 38 patients who experienced AKI, 20 (53%) had improvement in serum creatinine to less than 0.2 mg/dL above their baseline. When comparing for chronic kidney disease (CKD) stage, those with CKD I or II experienced AKI 17% of the time compared with 47% of the time in CKD III or worse (P = 0.005).

Conclusion: AKI was seen in nearly one-fifth of our patients, and patients with CKD stage III or worse are at increased risk. Although ledipasvir-sofosbuvir is generally safe in the general population, close monitoring of renal function is recommended. (Hepatology Communications 2018;2:1172-1178).

Hepatitis C virus (HCV) has an estimated global prevalence of 2%-3% with 130-170 million people infected with HCV.1 HCV causes chronic inflammation of the liver leading to chronic hepatitis, which can advance to liver cirrhosis and hepatocellular carcinoma and significant extrahepatic complications.2 Additionally, HCV has been shown to have a significant negative effect on a patient’s overall quality of life, including decreased work hours and productivity and increased health care costs.3 Cirrhosis and hepatocellular carcinoma related to HCV infection represent the most common indications for liver transplantation in the United States due to poor treatment options.4

Until recently, interferon-based treatments were the backbone of HCV treatment options.5 Unfortunately, therapy was only modestly effective and associated with significant side effects.6 Therefore, research has focused on HCV eradication using oral antiviral therapy. Recent clinical studies have demonstrated efficacy using the nucleotide analogue inhibitor sofosbuvir (Sovaldi; Gilead Sciences, Inc., Foster City, CA) as the backbone in treatment of nontransplant and posttransplant recurrent HCV.7 Both the ION-1 and ION-2

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; SVR, sustained virologic response.
trials demonstrated nearly 99% efficacy in the treatment of nontransplant, noncirrhotic HCV patients using sofosbuvir in a fixed-dose combination with the NS5A inhibitor ledipasvir (Harvoni, Gilead Sciences, Inc.), both with and without ribavirin.\(^8,9\) The side effect profile of ledipasvir/sofosbuvir (LDV/SOF) has been relatively mild and the drug has been well tolerated in trials, especially compared with previous interferon-based regimens.

The ION trials report that LDV/SOF therapy was primarily complicated by headaches or fatigue in approximately 10% of patients. Less frequently, patients experienced rashes, nausea, diarrhea, and insomnia. Serious side effects, such as nephrotoxicity, were not demonstrated by the ION-1 and ION-2 trials; however, these trials were conducted in a controlled clinical setting with rigorous exclusion criteria. Such trials are not always entirely reflective of the general patient population. Early data suggest possible risk of renal impairment during treatment with the use of LDV/SOF.\(^11\) LDV/SOF is mostly cleared renally,\(^10\) and given this, we studied the renal safety and rates of acute kidney injury (AKI) in patients with chronic HCV undergoing LDV/SOF direct acting antiviral therapy.

**Methods**

This single-center cohort retrospective observational study included all consecutive patients without history of liver transplants who initiated HCV treatment on LDV/SOF from October 1, 2014, to October 1, 2015. Patients were treated at Henry Ford Health Hospital in Detroit, Michigan, an urban, tertiary care center. All included patients completed 8, 12, 16, or 24 weeks of therapy with or without ribavirin and had available creatinine values before, during, and after therapy. All charts were reviewed by the authors. The institutional review board approved the study.

Background information including age, gender, race, BMI, degree of fibrosis or cirrhosis, HCV genotype, prior HCV treatment history, and date of treatments were collected. Baseline laboratory characteristics before treatment initiation included hemoglobin, white blood cell count, platelets, creatinine, international normalized ratio, aspartate aminotransferase, alanine aminotransferase, albumin, and total bilirubin. Patients were evaluated for hemoglobin nadir, peak creatinine while on treatment, as well as any adverse effects experienced while on therapy. All patients underwent routine lab draw at least every 4 weeks during treatment. More frequent lab draws were at the discretion of the prescribing clinician. Patients received courtesy calls if lab draws were missed. Posttreatment laboratory analysis included hemoglobin, creatinine, total bilirubin, aspartate aminotransferase, and alanine aminotransferase. All patients underwent posttreatment lab draws at 4, 12, and 24 weeks. HCV viral load was recorded prior to treatment initiation, at 4 and 12 weeks on treatment, at the end of treatment, and finally 4 and 12 weeks posttreatment to determine sustained virologic response (SVR12). An undetectable viral load on HCV RNA 12 weeks after completion of LDV/SOF was considered an SVR.

The primary endpoint of this study was the occurrence of AKI during antiviral therapy, defined as an increase of at least 0.3 mg/dL or at least 50% in serum creatinine level when compared with baseline values or more than a 25% reduction in estimated glomerular filtration rate (eGFR) when compared with baseline eGFR. eGFR was calculated using the abbreviated Modification of Diet in Renal Disease equation:

\[
\text{eGFR (mL/min/1.73 m}^2\text{) = 186} \times (\text{creatinine (mg/dL)} / 88.4) - 1.154 \times (\text{age})^{0.203} \times (0.742 \text{ if female})
\]

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The primary endpoint was considered reached if any single lab measurement was recorded above these thresholds. Clinically significant renal impairment was considered when patients reached the primary endpoint and had more than 50% reduction in eGFR. Normalization of renal function was considered if follow-up creatinine was no more than 0.2 mg/dL from baseline or eGFR was less than or equal to 25% of baseline eGFR. Each patient experiencing AKI was reviewed for urinalysis and/or renal biopsy to assess the mechanism of injury and/or alternative etiology of intertreatment renal injury.

Chronic kidney disease (CKD) was defined using the Kidney Disease Improving Global Outcomes definition. CKD stage I is defined as GFR ≥ 90 (mL/min/1.73 m²), CKD stage II is defined as GFR ≥ 60 ≤ 89 (mL/min/1.73 m²), CKD stage III is defined as GFR ≥ 30 ≤ 59 (mL/min/1.73 m²), CKD stage IV is defined as GFR ≥ 15 ≤ 29 (mL/min/1.73 m²), and CKD stage V is defined as GFR ≤ 15 (mL/min/1.73 m²).

Clinical data were compiled from the electronic medical record system. The data collected were expressed as means with SDs, medians with ranges, or as frequencies (percentages). For comparisons of CKD stages, a Student t test was used. Multivariable logistic regression analyses were used to assess factors associated with AKI. Clinical factors available that were deemed important and included in the analysis included age, race, sex, body mass index (BMI), CKD stage, cirrhosis history, HCV genotype, pretreatment hemoglobin, pretreatment white blood cell count, pretreatment serum albumin, and pretreatment serum total bilirubin. A P < 0.05 was considered statistically significant. Results are presented with an OR and 95% confidence intervals (CIs).

Results

A total of 306 charts of HCV-infected patients undergoing LDV/SOF treatment were initially reviewed. Of these, 105 had not completed therapy or did not have complete serum creatinine levels, 1 patient had end-stage renal disease and was on hemodialysis, and 3 patients died during treatment. These patients did not undergo further analysis.

A total of 197 patients were included in the final analysis. Table 1 depicts patient baseline demographics. The cohort consisted of 90 African Americans (45%), 78 Caucasians (40%), and 29 other or unspecified races (15%). Participants were predominantly male (59%) with a mean age of 60.8 years, who were also obese with a mean BMI of 28.1 kg/m². All patients were treated with LDV/SOF-based treatment. One hundred nine (55%)

![Table 1. Baseline Characteristics](image)

| Variable                 | Total (n = 197) |
|--------------------------|-----------------|
| Age, years               | 60.7 (9.3)      |
| Male                     | 117 (59%)       |
| BMI                      | 28.1 (4.7)      |
| Race                     |                 |
| Caucasian                | 78 (40%)        |
| African American         | 90 (45%)        |
| Other                    | 29 (15%)        |
| HCV genotype             |                 |
| 1                        | 189 (95%)       |
| 2                        | 5 (3%)          |
| 3                        | 3 (2%)          |
| Unknown                  | 1 (0.5%)        |
| Cirrhosis                | 72 (37%)        |
| Treatment type           |                 |
| Naïve                    | 109 (55%)       |
| Treatment experience     | 88 (45%)        |
| Treatment duration       |                 |
| 8 weeks                  | 14 (7%)         |
| 12 weeks                 | 133 (67%)       |
| 16 weeks                 | 1 (0.5%)        |
| 24 weeks                 | 49 (25%)        |
| CKD stage                |                 |
| I                        | 119 (60%)       |
| II                       | 63 (32%)        |
| III                      | 14 (7%)         |
| IV                       | 1 (0.5%)        |

Note: Data are presented as n (%) or means (SDs).

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![Table 2. Baseline Characteristics of Treatment Failures](image)

| Variable                     | Total (n = 11) |
|------------------------------|---------------|
| Male                         | 3 (27%)       |
| Treatment type               |               |
| Naïve                        | 7 (64%)       |
| Experienced                  | 4 (36%)       |
| Genotype                     |               |
| 1                            | 10 (91%)      |
| 2                            | 1 (9%)        |
| Cirrhosis                    | 8 (73%)       |
| CKD stage                    |               |
| I                            | 7 (64%)       |
| II                           | 2 (18%)       |
| III                          | 2 (18%)       |

Note: Data are presented as n (%).
patients were treatment naïve; 125 patients (63%) did not have evidence of cirrhosis; 14 patients (7%) underwent 8 weeks, 133 patients (67%) underwent 12 weeks, 1 patient (0.5%) underwent 16 weeks, and 49 patients (25%) underwent 24 weeks of treatment. Most patients were genotype 1 (95%); the remaining were genotype 2 (3%) and genotype 3 (2%). Of the patients treated, 63 (32%) were CKD stage II, 14 (7%) were CKD stage III, and 1 (0.5%) was CKD stage IV; the remaining 119 patients (60%) were CKD stage I.

All patients undergoing treatment achieved SVR at the end of treatment, of which 186 (94%) obtained SVR12 and were considered cured. There were 11 treatment failures, and baseline characteristics are found in Table 2. Of these failures, 7 (64%) were treatment naïve, 8 (73%) were female, 8 (73%) were cirrhotic, and 10 (91%) were genotype 1 with the remaining failure (1 patient) being genotype 2. With regard to renal function, 7 (64%) failures were CKD stage I, and 2 (18%) failures each were CKD II and III, respectively.
Of the 197 patients, 38 (19%) were diagnosed with AKI by a rise in creatinine of at least 0.3 mg/dL during treatment, as provided in Table 3. Four (11%) of the patients had AKI workup, all (100%) had bland urine sediment. No patients underwent further AKI workup with renal biopsy. An additional 4 patients (2%) had AKI at the end of treatment, for a total of 42 patients experiencing AKI during or at the completion of treatment. The mean creatinine levels before, during, and after antiviral treatment are shown in Fig. 1 for both the non-AKI cohort and the AKI cohort. Eighteen (25%) cirrhotic patients experienced AKI compared with 20 (16%) patients with no cirrhosis (P = 0.124). Of the 38 patients to experience AKI during treatment, 20 (53%) recovered and 18 (47%) had not recovered to less than 0.2 mg/dL serum creatinine greater than baseline at posttreatment week 12. Among the 38 who experienced intratreatment AKI, 6 (16%) of the patients had an eGFR reduction greater than 50% and were considered clinically significant for this study.

Of the 18 patients who did not recover to within 0.2 mg/dL of their pretreatment serum creatinine by posttreatment week 12, 6 (33%) recovered within 6 months of treatment. The remaining 12 (66%) had ongoing renal function loss at 6 months following treatment. Additionally, 16 (89%) patients who did not recover by posttreatment week 12 achieved SVR12. Of the remaining 2 who did not achieve SV12R (11%), 1 patient experienced renal recovery while the other did not.

An additional 64 (33%) had an eGFR reduction greater than 25% from baseline, of which 6 of 64 (9%) had more than a 50% reduction. At the end of treatment, 11 additional patients (6%) demonstrated more than a 25% reduction from baseline eGFR. Of the 64 who experienced reduced eGFR, 35 (55%) recovered to less than 25% from baseline eGFR. Of the 6 patients who experienced more than a 50% eGFR reduction, none completed treatment with a sustained reduction of more than 50%, 5 (83%) improved to less than 50% but more than 25% reduction, and 1 (17%) recovered to less than a 25% reduction.

With regard to preexisting renal impairment, 182 patients (93%) were CKD II or better defined by eGFR being 60 mL/min/1.73 m² or more, and 15 patients (7%) were CKD III or greater defined by eGFR being 60 mL/min/1.73 m² or less. Of the 15 patients with CKD III or greater, 7 (47%) were caused by hypertension, 4 (27%) were caused by diabetes, 2 (17%) were caused by both hypertension and diabetes, and 1 (7%) was caused by interstitial nephritis and hepatorenal syndrome type II, each.
Thirty-one patients (17%) with CKD I (23 patients; 19%) or II (8 patients; 13%) experienced AKI compared with 7 patients (47%) with CKD III (6 patients; 43%) or IV (1 patient; 100%) \( (P = 0.005) \) during treatment. An additional 3 patients with CKD I or II and 1 with CKD III or IV experienced AKI at the end of treatment. Of the 31 CKD I or II experiencing AKI during treatment, 18 patients (58%) had renal recovery compared with 6 patients (86%) with CKD III or IV \( (P = 0.227) \).

Multivariable logistic regression analysis showed that CKD III or greater \( (OR: 8.19, 95\% CI: 1.8-37.3, P = 0.007) \), male gender \( (OR: 3.32, 95\% CI: 1.19-9.26, P = 0.022) \), and age \( (OR: 1.08, 95\% CI: 1.02-1.15, P = 0.015) \) were significant predictors of AKI (Table 4).

Of the patients with preexisting CKD stage III or greater defined by eGFR being less than or equal to 60 mL/min/\( 1.73m^2 \), 13 of 15 (87%) patients achieved SVR12. Of the 7 intratreatment renal injuries, 5 (71%) patients improved to less than a 0.2 mg/dL increase from baseline serum creatinine.

**Discussion**

This study assessed the rates of renal impairment in patients undergoing HCV direct acting antiviral therapy with LDV/SOF in a diverse, urban practice. The ION trials demonstrated that LDV/SOF was well tolerated renally in a controlled clinical setting. Since its introduction, LDV/SOF has been extremely well tolerated in healthy populations. Patients with normal or minimal CKD have not demonstrated a reliable effect on renal function in clinical trials, and documented adverse effects have been limited to nonspecific complaints, such as fatigue, nausea, vomiting, and headaches.

Currently, there are limited published data suggesting the risk of AKI during oral direct acting antiviral treatment.\(^{11-13}\) These case reports and retrospective studies suggest an intrinsic cause of renal injury, with most of the available biopsies showing acute tubular necrosis (ATN) and acute interstitial nephritis (AIN). Most of these patients had returned to baseline renal function on cessation of LDV/SOF combination therapy. It is speculated that our population experienced either ATN or AIN, similarly to previous studies, as their mechanism of injury.

Our experience was largely consistent with this, as we found that a notable percentage of patients experienced a transient increase in creatinine during therapy, which could occasionally lead to a more than 50% decrease in patients’ eGFR. Patients with CKD III or worse were found to be significantly more at risk compared with those with CKD I or II. Although most patients demonstrated normalization of serum creatinine back to pretreatment baseline, a small cohort of patients had a persistent decrease in eGFR. These findings are certainly concerning and warrant further investigation and longer posttreatment follow-up to assess renal function, especially in patients who have prior renal insufficiency.

Previous studies have shown that co-use of nonsteroidal anti-inflammatory drugs (NSAIDs) and recurrent ascites were at increased risk for AKI during sofosbuvir-based antiviral therapy.\(^{12}\) Additionally, patients with cirrhosis are at increased risk from AKI from common etiologies such as hypovolemia, sepsis, and hepatorenal syndrome (HRS).\(^{14}\) Although our study showed no significant difference in AKI occurrence between cirrhotic versus noncirrhotic, we did observe a 9% absolute risk reduction. We admit that our study does not adjust for all confounders that may have contributed to AKI beyond LDV/SOF use, including preexisting hypertension or diabetes, co-use of NSAIDs, known ascites, and development of HRS. Although our study does adjust for available potential confounders, these additional factors either predispose patients to AKI or are known etiologies of AKI,\(^{12,14}\) and not having them available for analysis is a limitation of our study. Further investigation should attempt to account for these factors.

Only 11% of our patients underwent further investigations for other causes of renal injury with urinalysis, and no patients underwent renal biopsy to assess acute parenchymal changes, which is an additional limitation for our study as we are unable to rule out other etiologies.

In our experiences, we found that our efficacy and SVR12 rates closely correlate with the ION studies; however, there appears to be an underlying renal risk associated with LDV/SOF regimens that was not seen during the initial ION trials, especially in those with preexisting CKD stage III or worse, and is only now being demonstrated in less controlled, retrospective analyses. The large exclusion criteria of the ION trials may suggest why this renal risk is only now being unmasked in a less controlled, but more clinical, setting. We hypothesize that our patient population demographics was a significant contributor to the higher incidence of AKI. When compared with the original ION trials, our population was both older (60 years old compared with 52) and had a larger percentage of African Americans (45% compared with 19%).\(^{8,9}\)

Given these findings, there is a concern for potential renal complications associated with LDV/SOF-based
chronic HCV treatment. We do acknowledge that our sample size is limited and no definitive conclusions can be made regarding the role LDV/SOF plays in these transient eGFR decreases; furthermore, real-world data are required to accurately assess the safety profile of LDV/SOF.

Conclusions

In the treatment of chronic HCV infection, this large, single-center study observed AKI in 19% of our patients during treatment with LDV/SOF. Although renal impairment was seen nearly one-fifth of the time, most (61%) of those patients had transient improvement in renal function before completion of therapy. A significant greater incidence of AKI rates was identified for those with CKD III or worse compared with those with CKD II or better, although the presence of cirrhosis or not was not significant in the development of AKI. Although close renal monitoring is necessary, LDV/SOF treatment for chronic HCV infection overall appears to be safe. We suggest that prescribers closely monitor renal function and remain vigilant of renal impairment throughout treatment duration, especially for those with baseline renal impairment.

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