Journal of Cardiovascular Disease Research

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Effects Of Direct Acting Antivirals on Glomerular Filtration Rates and Neutrophil Gelatinase-Associated Lipocalin During Treatment of Hepatitis C Patients

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Abstract

Background

Direct acting antivirals (DAA) havesignificantly contributed to the treatment protocol for chronic hepatitis C (CHC), nonetheless, there are concerns regarding their safety especially in patients with chronic kidney disease (CKD). Neutrophil gelatinase-associated lipocalin (NGAL) is an emerging biomarker for renal tubular injury. Herein, we aimed to estimate the changes in serum NGAL levelsfollowing DAA-therapy, as well as to investigate the diagnostic reliability of serum NGAL in case of potential DAA-related nephrotoxicity. We consecutively enrolled 80treatment-naïve adult CHC patients who were eligible for DAA-therapy. We further categorizedthe patients into 2 groups, group I included 40 patients with normal kidney functions who received SOF/DAC for 12-weeks, whereas group II included 40 CKD patients who received OBV/PTV/r + RBV for 12-weeks. In addition, 20 healthy participants with matched age and sex were enrolled as controls.The serum NGAL level was measured at baseline and at the end of therapy(EOT) using an Enzyme-Linked Immunosorbent Assay (ELISA).

Results

At EOT compared to baseline, serum NGAL levels were significantlydecreased in group I (271 ± 77.24 *vs* 167.3 ± 89.19 ng/mL, P<0.001) and group II (471.45 ± 97.42 *vs* 360.1 ± 122.81 ng/mL, P<0.001), along with steady levels of serum creatinine as well as eGFR. Serum NGAL levels were negatively correlated with eGFR at baseline and EOT in group II (r = -0.928 and -0.728, respectively, P< 0.001). NGAL serum level at a cut-off value > 342 ng/mL had97.22%sensitivityand97.73%specificity in predicting patients with KDIGO-CKD stage >2.

Conclusion

DAA are not only safe to use in CKD patients, but also has an additive beneficial effect on the renal tubules *via* HCV eradication as indicated by the significant decline in serum NGAL levels.

Key words

Antiviral agents; Hepatitis C virus; Inflammation; Neutrophil Gelatinase-Associated Lipocalin Protein; Kidney Tubule; Sofosbuvir; Paritaprevir; Acute Kidney Injury

I-BACKGROUND

The infection with hepatitis C virus (HCV) is an independent risk factor for increased incidence of chronic kidney disease (CKD)[1,2].Moreover, it is associated with an acceleratedecline in the estimated glomerular filtration rate(eGFR)[3,4], impaired quality of life[5], and increased rates of morbidity as well as mortality in CKD patients[6,7,8]. These data justifythe importance of HCV eradication in CKD patients;however, the treatment of HCV in these patients is challenging either due to impaired renal drug elimination oraltered drug clearance in patients on dialysis.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Treatment options forpatients with chronic hepatitis C (CHC)and CKD stage 4-5 were unsatisfactory due to frequent adverse events (AEs)caused bypegylated interferon (PEG-IFN), ribavirin (RBV), and first-generation protease inhibitors[9,10,11].

It is noteworthy that the novel direct-acting antiviral (DAA) therapiesare more efficientwith fewer AEsthanprevious therapies[12,13]; however, the current knowledge regarding the safety and efficacy of DAA-regimens in patients with CKD-stage 4-5 is controversial[14,15].

Sofosbuvir(SOF) is a pan-genotypic HCV NS5B polymerase inhibitor. GS331007, which is the active metabolite ofsofosbuvir, is renally eliminated.Therefore, concerns have been raisedregardingits potentialnephrotoxicityparticularly in CKD patients[16,17].Hence,it waspreviously recommended to avoid SOF in patients with eGFR ≤30 mL/min/1.73m^2[18].However, recentrecommendations reconsideredseveral reports of SOF safety in patientswith eGFR < 30 mL/min/1.73m^{2}or on dialysis[14,19-24].Daclatasvir (DAC) (NS5A inhibitor) is mainly metabolized by the liver[25]. Moreover, no significant data were reported regardingRBV nephrotoxicity[26].

The 2-DAA regimen of ombitasvir (NS5A inhibitor)/ritonavir-boosted paritaprevir (NS3/4A inhibitor) plus RBV(OBV/PTV/r + RBV) is a treatment regimen for CHCpatients with CKD because the metabolism of these drugs is mainlyhepatic mediated[27-30].

Currently, serum creatinine and eGFR are the only laboratory parameters used tomonitorthe renal functions during DAA-therapy[31].Actually,eGFR may be unreliable surrogate for renal functions in conditions like liver cirrhosis and drug induced nephrotoxicity[32].Consequently, it is recommended to use a complementary marker for renal impairment in addition toserum creatinine and eGFR[31].

Neutrophil gelatinase associated lipocalin (NGAL) is a glycoprotein secreted by epithelialand haematological cells. It is filtered into the glomerulus and reabsorbed by theproximal tubules[33]. It was identified as an earlymarker foracute kidneyinjury (AKI) in several clinical circumstances and drug-induced nephrotoxicity[34-37].Moreover, NGAL was a reliable marker ofrenal functions in CHC patients and cirrhosis[33,38,39].

However, the diverse findings of recent studies have led to acontroversy regarding the potential clinical utility of NGAL in CKD patients[36,40-43].Consequently, we aimed to estimate the changes in serum NGAL levels following DAA-therapy, as well as to investigate the diagnostic reliability of serum NGAL in case of potential DAA-related nephrotoxicity.

II-METHODS

This prospective observational study was conducted at the Viral Hepatitis Treatment and Research Centre, Ain Shams University, Cairo, Egypt, from October 2018 to June 2020. We consecutively enrolled 80treatment-naïve adult CHC patients who were eligible for DAA-therapy. We further categorizedthe patients into 2 groups,group I included 40 patients with normal kidney functionswho received SOF/DAC for 12-weeks, whereasgroup II included 40 CKD patients whoreceivedOBV/PTV/r + RBV for 12-weeks.In addition, 20 healthy participants with matched age and sex were enrolled as controls.

Exclusion criteria were applied to treatment experienced patients, patients with other causes of hepatic disease, co-infection withhepatitis B virus or human immune deficiency virus, hepatocellular carcinoma, sepsis, malignancies, pregnant women, and patients on regular haemodialysis.

SVR12 was described as an undetectable HCV-RNA 12-weeks after the end of treatment (EOT)[18].

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki. The study was approved by the Ethical Review Board of Ain Sham University (Reference Number:FMASU MD 325/2018).All participants applied an informed written consent prior to inclusion in the study.

Calculations

eGFR was calculated at baseline and EOT using the Chronic Kidney Disease EpidemiologyCollaboration (CKD-Epi) equation[44].

The KDIGO-CKD classification was used to classify the patients according to the CKD grade at baseline[31].

Liver fibrosis was estimatedby fibrosis 4(FIB-4) score[45]and AST to platelet ratio index (APRI)[46].

NGAL measurement

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

We measured serum NGAL at baseline and EOT usingthe human NGAL enzyme linked immunosorbent assay (ELISA) kit (BioassayTechnology Laboratory, Catalogue No. E1719Hu,Shanghai, China) with reference range = 5-600 ng/mL and sensitivity = 2.01 ng/mL.

Statistical analysis

All results were collected, tabulated, and statistically analysed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.Data were presented as frequency and percentage for categoricalvariables, mean and standard deviation (SD) for parametric numericalvariables, and median [interquartile range (IQR)] for non-parametric numerical variables. Student *t*-test, Mann-Whitney test, Chi-Square test, or Fisher's exact test was used as appropriate.Variables were compared before and after therapy using a paired *t*-test or One-way ANOVA (for parametric numerical data), orMcNemar test (for nominal data). Correlation analysis between serum NGALand other variables was done usingSpearman's rho or Pearson's method as appropriate. Receiver-operating characteristics (ROC) curveanalysis was used to evaluate the diagnostic performance of NGAL for the differentiation of KDIGO-CKD stage > 2. A two-tailed $P < 0.05$ was considered significant.

III-RESULTS

This study included 80 CHC patients, 47 (58.75%) males and 33 (41.25%) females with a mean age of 57.03 ± 15.46 years. The control group included 20 healthy subjects, 13 (65%) males and 7 (35%) females with a mean age of 53.6 ± 1.57 years. The baseline characteristics of group I and II are shown in Table 1.

All patients completed the scheduled DAA-regimen and achieved SVR12. DAA-therapy was tolerated in patients from both groups without any episodes of serious AEs or AKI. The AEs were comparable between the two groups, and the most common encountered AEs were gastrointestinal symptoms (12%), anaemia (9%), headache (7%), and fatigue (6%).

At baseline, patients had significantly higher serum NGAL levels compared to controls (371.23 ± 133.43 *vs* 73.85 ± 21.81 ng/mL, $P< 0.001$). Additionally, group II patients had significantly higher serum levels of NGAL than group I patients (Table 2, Figure 1). Serum NGAL levels decreased significantly in patients of both groups at EOT (Table 2, Figure 1). Similar results were reproduced when we ranked group II patients according to the KDIGO-CKD stage (Table 3, Figure 2). In contrast, no significant changes in serum creatinine levels and eGFR were observed at EOT in patients from both groups (Tables 4-6).

In group II, serum NGAL levels were negatively correlated with eGFR at baseline and EOT ($r = -0.928$ and -0.728, respectively, $P < 0.001$) (Figure 3). In both groups, serum NGAL was positively correlated with age (Table 7).

By ROC curve analysis, serum NGAL at a cut-off value ≥ 342 ng/mL had AUC = 0.975, sensitivity of 97.22%, specificity of 97.73%, 95% CI = 0.913 - 0.997, and P value ≤ 0.0001 for the differentiation of KDIGO-CKD stage >2 (Figure 4).

Table 1 Baseline patients' characteristics of group I and II

Variables		Group I (n = 40)	Group II (n = 40)	*p* value
Age (years)		54.43 ± 13.44	59.63 ± 12.98	0.310
Gender	Male	25 (62.5%)	22 (55%)	0.496
	Female	15 (37.5%)	18 (45%)	
BMI (kg/m^2)		26.57 ± 4.82	28.97 ± 5.69	0.045
Diabetes mellitus		2 (5%)	7 (17.5%)	0.154
Hypertension		5 (12.5%)	15 (37.5%)	0.010
MELD score		7.5 ± 1.63	15.83 ± 4.11	< 0.001
Child-Pugh score	A	39 (97.5%)	40 (100%)	0.161
	B	1 (2.5%)	0 (0%)	
KDIGO-CKD stage	2		4 (10%)	
	3a		7 (17.5%)	

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	3b		11 (27.5%)	
	4		13 (32.5%)	
	5		5 (12.5%)	
	Grade 1		5 (26.32%)	
Grade of nephropathy by ultrasound	Grade 2		6 (31.58%)	<0.001
	Grade 3		6 (31.58%)	
	Grade 4		2 (10.53%)	
HCV PCR (IU/mL)		724890.5 (140182.5 - 1820605.5)	465061.5 (122098.5 - 2123854.4)	0.441
TLC (10^9/L)		6.78 ± 2.51	7.47 ± 2.72	0.238
Haemoglobin (g/L)		136.8 ± 18.3	123.7 ± 16.6	0.001
Platelets (10^9/L)		243.15 ± 86.83	233.13 ± 81.48	0.596
ALT (IU/L)		34 (26.5 - 45.5)	24.5 (16.5 - 40)	0.032
AST (IU/L)		33 (26.5 - 48)	29 (24 - 37.5)	0.088
Total bilirubin (mmol/L)		0.01 ± 0.006	0.01 ± 0.005	0.399
Serum albumin (mmol/L)		0.63 ± 0.07	0.59 ± 0.07	0.007
INR		1.08 ± 0.1	1.06 ± 0.07	0.265
FIB-4 score		0.96 (0.69 - 1.44)	1.10 (0.99 - 2.16)	0.132
APRI score		0.35 (0.2 - 0.6)	0.3 (0.2 - 0.5)	0.483

TLC: Total leucocytic count, ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio; FIB-4 score: Fibrosis score; APRI score: AST to platelets ratio index

Table 2 Serum NGAL levels at baseline and end of therapy in group I and II

		Group I	Group II	*p* value
Serum NGAL levels (ng/mL)	Baseline	271 ± 77.24	471.45 ± 97.42	<0.001
	EOT	167.3 ± 89.19	360.1 ± 122.81	<0.001
p value		<0.001	<0.001	

Table 3 Baseline and EOT serum NGAL levels in group II patients according to KDIGO-CKD classification

KDIGO-CKD stage	Serum NGAL level (ng/mL)		*p* Value
	Baseline	EOT	
2	297 ± 30.7	241 ± 155.17	0.444
3a	404 ± 29.23	300.29 ± 81.08	0.016
3b	432.91 ± 49.29	331.27 ± 119.65	0.011
4	550.62 ± 41.64	430.62 ± 93.69	<0.001
5	584.4 ± 21.65	419.2 ± 117.23	0.027

		Group I	Group II	*p* value
Serum creatinine level (mmol/L)	Baseline	0.07 ± 0.01 (0.88 mg/dl±0.2)	0.26 ± 0.12 (2.95 mg/dl±1.46)	< 0.001
	End of therapy	0.07 ± 0.02 (0.9 mg/dl±0.23)	0.25 ± 0.12 (2.88mg/dl±1.39)	< 0.001
*p*value		0.527	0.621	

Table 4 Serum Creatinine levels at baseline and end of therapy in group I and II

Table 5 eGFR at baseline and end of therapy in group I and II

		Group I	Group II	*p* value
eGFR (mL/min)	Baseline	109.85 ± 29.63	35.1 ± 18.36	<0.001

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	End of therapy	107.13 ± 30.82	35.53 ± 19.52	<0.001
p value		0.592	0.718	

Table 6 eGFR at baseline and EOT according to KDIGO-CKD classification in group II patients

Table 7 Correlation analysis of serum NGAL levels with patients' laboratory parameters at baseline in Group I and

KDIGO-CKD stage	eGFR (mL/min)		*p* Value
	Baseline	EOT	
2	72.25 ± 7.59	71.5 ± 25.49	0.949
3a	51.14 ± 5.08	50.43 ± 9.34	0.691
3b	37.64 ± 4.25	38.73 ± 6.47	0.564
4	21.69 ± 4.84	21.69 ± 6.26	1.000
5	12.2 ± 0.84	14.8 ± 2.49	0.065

II

Parameters	Group I		Group II	
	r	*p* value	r	*p*value
Age	0.399	0.01	0.318	0.026
BMI	0.056	0.732	-0.251	0.168
HCV PCR	0.274	0.087	-0.112	0.490
TLC	0.046	0.778	0.213	0.187
haemoglobin	0.108	0.508	-0.029	0.859
Platelets	-0.176	0.278	0.019	0.908
ALT	0.014	0.931	0.014	0.933
AST	-0.016	0.924	-0.145	0.059
Total Bilirubin	-0.076	0.641	0.051	0.757
Serum albumin	-0.063	0.699	0.174	0.284
INR	0.206	0.203	-0.060	0.712

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; HCV PCR: Hepatitis C virus polymerase chain reaction; INR: International normalized ratio; TLC: Total leucocytic count;

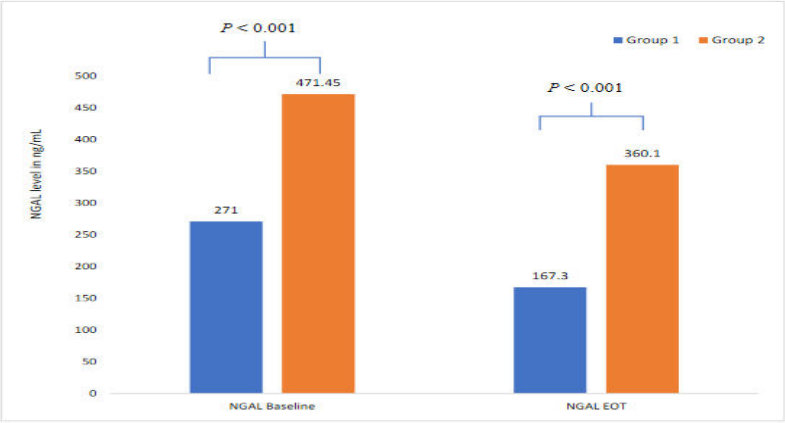

Figure 1 Serum NGAL levels in group I and II at baseline and end of therapy (EOT)

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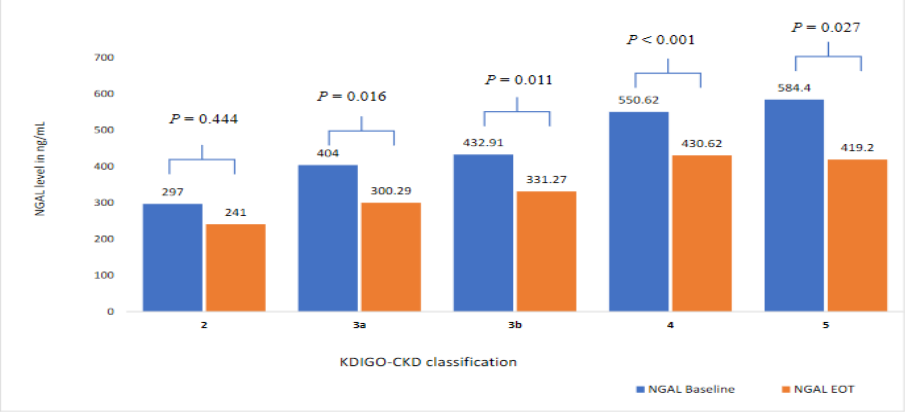

Figure 2 Serum NGAL levels in group II at baseline and end of therapy (EOT) according to KDIGO-CKD classification

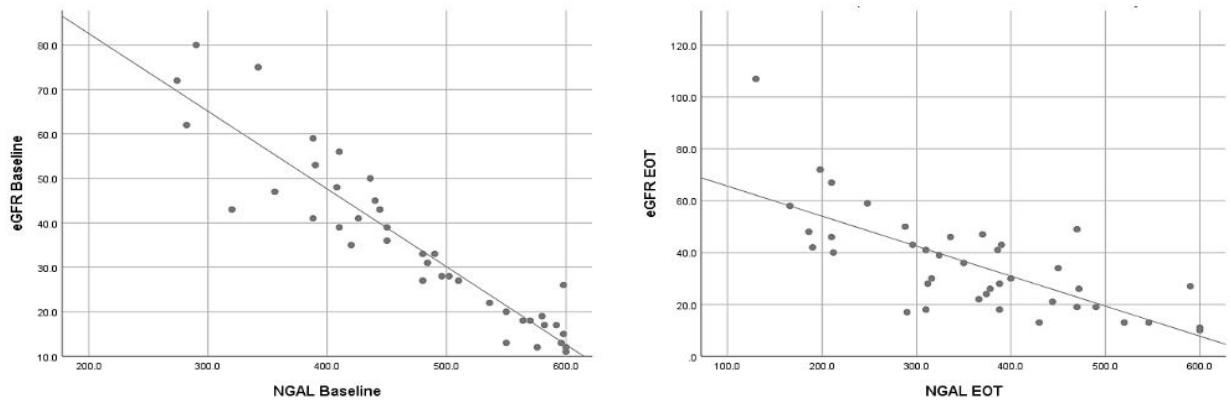

Figure 3 The correlation between serum NGAL levels and eGFR at baseline and end of therapy (EOT) in group II

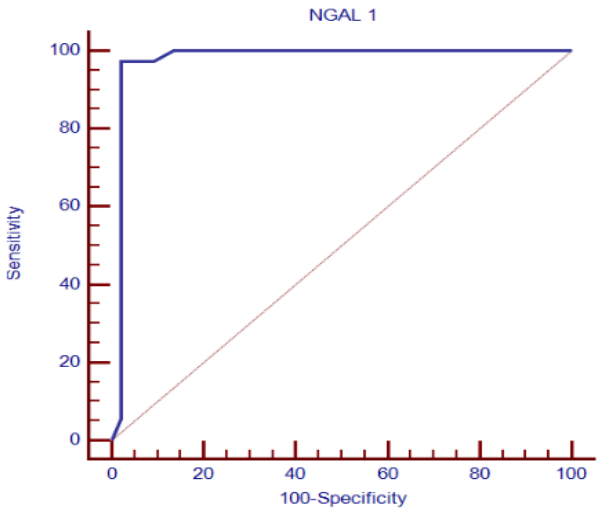

Figure 4 ROC curve for the diagnostic performance of NGAL for detecting patients with KDIGO-CKD stage >2 in group II

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

IV-DISCUSSION

HCV-related kidney disease is mainly presented as a glomerular disease[47]. However, HCV core proteins were isolated from both glomerular and tubular tissues, suggesting the presence of a concomitant tubulointerstitial involvement[48].

NGAL is mainly a tubular renal marker[49,50].In addition, elevated NGAL levels were also observed in cases of epithelial damage and inflammation[33,51,52].

To date, conflicting data have been raised regarding the association between HCV and inflammation. Indeed, some studies indicatedthe pro-inflammatory capacity of HCV RNA[53,54]. Additionally, the functional response of natural killer cells to IFNα was enhanced by DAA-therapy[55]. Nonetheless, further studies are mandatory to explore the underlying mechanism of the balance between the pro- and anti-inflammatory responses through different immunological and inflammatory biomarkers, including NGAL, during HCV infection and after viral eradication by DAA-therapy[56].

Thus, it is challenging to predict the impact of DAA-therapy on serum NGAL levels.Since DAA-therapy is expected to havean affirmative effect on renal function throughHCV eradication from glomerular and tubular cells[48], andconversely, the alteredbalance of the inflammatory processesdeveloped during treatment and aftereradication of HCV[56,57].

The current literature regarding NGAL levels after DAA-therapy has reported conflicting results[38,40-43].Consequently, we aimed to estimate the changes in serum NGAL levels following DAA-therapy, as well as to investigate the diagnostic reliability of serum NGAL in case of potential DAA-related nephrotoxicity.

All patients completed the scheduled DAA-regimen.DAA-therapy was tolerated in patients from both groups without any episodes of serious AEsor AKI.These findings demonstrate the safety as well as tolerability of DAA-regimens even the sofosbuvir-based in CKD patients as previously reported[14,41].

In consistence with previous results[38,40], our patients had significantly higher serum levels of NGALthan control group. Additionally, group II patients had significantly higher serum levels of NGAL than group I patients. Interestingly, after achieving SVR, serum NGAL levels decreased significantly along with steady serum creatinine and eGFR in patients from both groups. This decline was reproduced when the patients of group II were classified according to the CKD-grade. These findings prove the beneficial role of DAA-therapy in eliminating the deleterious effect of HCV on renal tubular cells and the renal safety of DAA-regimens utilized in our study[14,22]. The same result was reported by Nada et al[40] after 12-weeks of SOF/DAC± RBV therapyin 87 patients with CKD grade 1-3a.

In contrast,Strazzullaet al[38]detected a significant increase in serum NGAL levels at EOT along with stable eGFR. Their studyincluded only 8 patients with CKD grade 1-2,2 patients received simeprevir/daclatasvir for 24 weeks andsix patients received PEG-IFN/RBV/telaprevir for 12-weeks followed by PEG-IFN /RBV for a further 24-weeks.In their subsequent retrospective study[41], they reported the same results in 18 patients with CKD grade 1-3a who received sofosbuvir/ledipasvir regimen.They attributed their results to either drug induced tubular injury[58,59]or induction of the inflammatory response by antiviral treatment[53-56].The discrepancy between our results and those of Strazzullaet al[38,41]is probablydue to the differences in study design, sample size, and the DAA-regimen used.

In agreement with our results, Strazzullaet al[38]detected a positive correlation between NGAL and age. This correlation is predictable and consistent with the renal structural and functional changes with aging[60,61].

Similar to previous reports[38,62], we detected a statistically significant negative correlation between serum NGAL levels and eGFR at baseline and SVR in group II patients, thus proving the hypothesis that HCV-related renal disease is not only a glomerular disease, but alsoit contains a tubulointerstitial component through the direct cytopathic injury causedby HCV core proteins deposition in both glomerular and tubulointerstitial tissues[48,63].

In consistence with the published literature[38,40], no significant correlation was detectedbetween serum NGAL levelsand HCVviral load. This wascompatible with the hypothesis that occult HCV infection may cause renal diseaseeven with undetectable HCV RNA[64,65].

By ROC curve analysis, serum NGAL at a cut-off value ≥ 342 ng/mL had AUC = 0.975, 97.22% sensitivity, 97.73% specificity, and P value ≤ 0.0001 for the differentiation of KDIGO-CKD stage >2. Also, Zhang J et

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

al[66]reported 90.2% sensitivity and 89.5% specificity when using serum NGAL for the detection ofAKI.Moreover, it wasreported that plasma NGAL ata cut-off value of 62 ng/dL had 98.1% sensitivity and 91.9% specificity for the diagnosis of AKI after cardiopulmonary bypass[67]. These results indicate the diagnostic reliability of NGAL for the prediction of renal impairment.

To our knowledge, this is the first report ofchanges in serum NGAL levels in CKD patients including grade 4-5 who received OBV/PTV/r + RBV regimen. However, large-scale studies with longer follow-up duration are needed to determine whether HCV eradication with DAA-therapy has a long-term beneficial effect on renal functions and to determine the ultimate clinical utility of NGAL in CKD.

V-CONCLUSIONS

We can conclude thatDAA are not only safe to use in CKD patients, but also has an additive beneficial effect on renal tubules *via* HCV eradication as indicated by the significant decline in serum NGAL levels.

List of abbreviations

AKI: Acute kidney injury; AEs:Adverse events; APRI: AST to platelet ratio index; CHC: Chronic hepatitis C; CKD: Chronic kidney disease; CKD-Epi: Chronic Kidney Disease Epidemiology; DAC:Daclatasvir; DAA: Direct-acting antiviral; EOT: End of treatment; eGFR:Estimated glomerular filtration rate; FIB-4 score:Fibrosis 4 score;HCV: Hepatitis C virus; NGAL:Neutrophil gelatinase associated lipocalin; PEG-IFN: Pegylated interferon; RBV: Ribavirin; SOF:Sofosbuvir

Declarations

Ethics approval and consent to participate

Approval was obtained from the Ethics Committee of Faculty of Medicine, Ain Shams University (FMASU MD 325/2018). Informed written consent was obtained from each participant before enrollment in the study. This study was performed in accordance with the 1975 principles of the Declaration of Helsinki and its appendices.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

MN, EN, AE, GN, WHdesigned the research; MN participated in the acquisition of data;MN, EN, AE, GN, WHparticipated in the analysis and interpretation of the data;EN, AE, GN, WHrevised the article critically for important intellectual content; GM, WHwrote the manuscript.All authors have read and approved the manuscript.

Acknowledgments

Not applicable

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