CD86/Programmed Death-Ligand-1 as a Predictor Ratio for Response to Directly Acting Antiviral Therapy of Chronic Hepatitis in Egyptian Patients

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Research Article

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Abstract

Objectives:

Predictors of direct-acting antivirals response of HCV serve as assessment methods and help to treat doctors identify patients who are likely or unlikely to SVR.

Methods:

Egyptian chronic hepatitis C patients (N=300) were divided into 2 groups with 150 patients each. Group 1: received triple therapy (Sofosbuvir, Pegylated interferon, and ribavirin) for 12 weeks. Group 2: received dual therapy (Sofosbuvir and ribavirin) for 24 weeks. For all patients, routine blood markers, extracellular matrix markers, and dendritic cell markers were done. Hyaluronic acid, Collagen IV, Procollagen III peptide, laminin, platelet-derived growth factor and tissue inhibitor of metalloproteinase-1, were all performed using ELISA. Dendritic cells Co-stimulatory markers (CD40, CD83, and CD86), and co-inhibitory marker (PD-L1) were evaluated by real-time PCR.

Results:

SVR is associated with a decrease in the extracellular matrix markers and dendritic cell markers. AST/ALT ($p=0.003$), Fibroscan ($p=0.024$), CDs co-stimulatory markers and PD-L1 ($p=0.05$ - $p<0.0001$) were differentiated between responders and non-responders. Using multivariate analysis exhibited that the decrease in PDL1 levels was significant ($p=0.012$) and increase significant ($p=0.024$) in CD86 associated with SVR. CD 86/ PDL-1 ratio had an AUC of 0.82 for prediction SVR.

Conclusions:

Baseline CD 86/ PDL-1 ratio was the only marker predicting SVR.

Introduction

Global, CHC with HCV is related to substantial morbidity and mortality [1]. About 170 million individuals are assessed to be diseased with HCV [2]. CHC is a main public health problem in Egypt, where it bears the uppermost occurrence rate in the world [3]. In Egypt, the HCV administration program aimed to reduce the HCV prevalence ($<2\%$) within ten years and $<1\%$ by 2030 [4]. The treatment of HCV with DAA gives 90% SVR rates [5]. Second-generation DAAs (sofosbuvir, daclatasvir, and simeprevir) have been developed to provide more effective treatments for HCV than the first generation of DAAs (boceprevir and telaprevir) [6]. It is important to identify key predictors of response of HCV treatment and parameters that can be used to tailor treatment decisions [7]. Several studies evaluated viral and patient-related factors for pretreatment prediction of SVR rates for IFN [8]. Non-invasive markers that reflect the change in liver cells structure or functions liver and the SVR would be preferable [9]. In hepatic fibrosis, there is a difference between the production and analysis of the extracellular matrix. The extracellular matrix is composed of collagens, the non-collagenous glycoproteins (hyaluronic acid, laminin, and fibronectin).

These markers are secreted by the liver cells and elevated in hepatic fibrosis [10–14]. DCS is the most powerful antigen-presenting cell and HCV infection altered many DCs functions. In HCV infection, alternations of DCs functions lead due to changes of major histocompatibility complex and co-stimulatory molecules. This led to weak T cell response and partially controls SVR [15]. This study aimed to evaluate baseline routine markers and extracellular matrix markers, DCs Co-stimulatory markers, and PD-L1 can be used as predictors of SVR.

Materials And Methods

Study participants

This study included 300 non-selected HCV-infected patients, consecutively treated from the National Hepatology and Tropical Medicine Research Institute, Kasr Al-Ainy, Faculty of Medicine, Cairo University. The CHC patients selected had to conform to the following inclusion criteria: detectable anti-HCV antibody and detectable serum HCV-RNA (COBAS Ampliprep/ COBAS TaqMan, Roche Diagnostics, Pleasanton, USA). Hepatic fibrosis staging was examined using FibroScan [16]. All patients were negative for hepatitis B surface antigen and HIV test. Other causes of hepatocellular injury were excluded. All patients were classified into two subgroups (G) every 150 patients: Group 1: received triple therapy (Sofosbuvir, peg INF, and ribavirin) for 12 weeks. Group 2: received dual therapy (Sofosbuvir and ribavirin) for 24 weeks. SVR was defined as negative HCV-RNA post-triple and dual treatment. Fasting ten ml of blood samples were withdrawal from all patients and divided into three parts. The first part was treated with EDTA for assessment of HbA1C, platelet count, DCs Co-stimulatory markers, and PD-L1. The second part was treated with sodium citrate for prothrombin-INR. The third part left to coagulation and serum was separated for evaluation of baseline routine markers and extracellular matrix markers. The study was accepted by the local ethics committee and the Ethics guidelines of the 1975 Declaration of Helsinki were applied in this study. Informed consent was collected from each patient.

Biochemical assays

The liver profile was tested on an automated biochemistry analyzer (A15, Biosystem, Spain). Complete blood count was tested using a KX-21 Sysmex automated hematology analyzer (Sysmex Corporation, Kobe, Japan). Alpha-fetoprotein (AFP) was assessed by chemiluminescence, with Immulite (1000) AFP kit (Diagnostic Products Corporation; Los Angeles, CA, USA). Hyaluronic acid, Collagen IV, Procollagen III peptide, laminin, platelet-derived growth factor (PDGF), tissue inhibitor of metalloproteinase-1 (TIMP-1), and collagen IV (Shanghai Sunred Biological Technology Co., Ltd, Shanghai, China) were done according to the Attallah et al [17, 18]. Fold changes of CD83, CD86, CD40, and PD-L1 in peripheral blood mononuclear cells were determined according to [15].

Statistical analysis

Statistical analyses were performed by SPSS software v.22.0 (SPSS Inc., Chicago, IL) and Graph Pad Prism package; v.5.0 (Graph Pad Software, San Diego, CA). Qualitative data were evaluated using Chi-

square t for categorical variables and presented as numbers and percentages. Quantitative data were tested for normality distribution using the Kolmogorov-Smirnov test. Parametric data were tested using the ANOVA test or t-test and presented as mean $\pm$ standard deviation. Non-parametric data were tested using the Mann-Whitney test and presented as median (Interquartile range). Correlations test was done using Pearson's test for parametric data and spearman for non-parametric data. Univariate analyses were done for baseline routine markers and extracellular matrix markers, DCs Co-stimulatory markers, and PD-L1 then evaluated significant biomarkers using multivariate analyses. The independent discriminative values of significant variables for the SVR were assessed by receiver-operating characteristic (ROC) curves and stepwise linear discriminant analysis. In the second step, to calculate a ratio positive correlation parameter (CD 86) was put in the numerator and negative correlation parameters (PDL1) in the denominator [19]. Common indicators of CD 86- PDL1 ratio performances were presented.

Results

Univariate analysis of laboratory markers

After dual and triple treatment, 266 patients were responders and 27 non-responders, and 7 patients were missed and were excluded from further analysis. At the end of treatment, the SVR (138/146) was higher (95%) in triple treatment patients than patients (128/147) who had received dual treatment (87%) with significant differences ($p = 0.02$). Baseline routine biochemical markers and histological stages for responders and non-responders patients were presented in Table 1. The chief endpoint of this study was the developed ratio with discriminating responders and non-responders patients. To determine which markers could distinguish responders and non-responders patients, the routine blood markers, extracellular matrix markers, and dendritic cell markers of these two groups were examined. Except AST/ALT ($p = 0.003$). Baseline levels of extracellular matrix markers were higher in non-responders than responder patients (hyaluronic acid, collagen IV, PDGF-BB, Procollagen III peptide, laminin, TIMP-1, and PDGF-BB) without significant differences. There were significant decrease in FibroScan score ($p = 0.024$), all co-stimulatory markers and PDL1 ($p = 0.05 - p < 0.0001$) in responder patients in comparison to non-responder patients; Table 2.

Table 1
Clinical data of responder and non-responder after dual and triple HCV treatment.

Variables	Responders (N = 266)	Non-Responders (N = 27)	<i>P value</i>
Age	52.8 ± 10	51.7 ± 11.1	0.63
Sex (F/M)	157/109	15/12	0.84
AST (U/L)	30.0 (23–54)	34.0 (21.0–42.0)	0.417
ALT (U/L)	27(25–35)	33 (23–42)	0.62
AST/ALT ratio	1.0 (0.8–1.3)	1.2 (0.7–1.3)	0.003
Total bilirubin (mg/dl)	0.87 ± 0.37	0.92 ± 0.4	0.55
Albumin (g/L)	38.7 ± 5.3	38.2 ± 5.1	0.44
AFP (U/L)	6.3 (4–13)	9.0 (4–19)	0.43
Platelet count (10 ⁹ /L)	168 ± 71	152 ± 55	0.23
APRI	1.1 ± 0.61	1.2 ± 0.61	0.32
Prothrombin-INR	1.1 ± 0.12	1.2 ± 0.12	0.58
FBS (mg/dl)	109 ± 37.5	112 ± 31.6	0.87
HbA1C (%)	6.0 ± 1.0	5.5 ± 1.2	0.162
F0 (No, %)	28 (10.5%)	0 (0%)	0.17
F0-F1 (No, %)	6 (2.3%)	0 (0%)	
F1 (No, %)	21(7.9%)	0 (0%)	
F1-F2 (No, %)	23(8.6%)	3 (11.1%)	
F2 (No, %)	12 (4.5%)	0 (0%)	
F3 (No, %)	44(16.5%)	7 (25.9%)	
F3-F4 (No, %)	19 (7.1%)	4(14.8%)	
F4 (No, %)	113 (42.5%)	13(48.1%)	

Table 2
Baseline levels of dendritic cell markers and extracellular matrix markers associated with response for dual and triple HCV treatment.

Variables	Responders	Non-Responders	P value
Fibroscan (kPa)	107.2 (71.0- 121.3)	131.3 (83.1- 131.3)	0.024
Hyaluronic acid (ng/mL)	113.0 (80.1-165.6)	121 (86.8-148.3)	0.98
Procollagen III peptide (ng/mL)	17.6 (13.2–22.4)	18.5 (13.7–26.6)	0.25
Collagen IV (µg/mL)	7.3 (5.9–9.9)	8.0 (5.9–13.9)	0.35
Laminin (ng/mL)	88.8 (68.8-112.1)	87.7 (74.4-127.8)	0.36
TIMP-1 (ng/mL)	12.3 (7.9–18.4)	13.5 (11.0-28.8)	0.47
Platelet Derived Growth Factor -BB	115.5 (92.6-146.2)	125.0 (85.4-192.5)	0.51
Programmed death-ligand 1	0.15 (0.01–0.75)	0.98 (0.179–2.93)	< 0.0001
CD40	0.89 (0.29–2.1)	0.43 (0.023–1.24)	0.04
CD83	0.67(0.12–1.4)	0.28 (0.03–0.80)	0.017
CD86	0.76 (0.14–2.1)	0.08 (0.015–0.73)	< 0.0001
CD86/PDL-1	3.8 (0.73–21.2)	0.23 (0.01- 1.0)	< 0.0001

Evaluation of diagnostic performances of significant markers to predict SVR using the area under ROC

PDL-1 was the most effective marker among univariate significant markers (AST-ALT ratio, FibroScan score, DCs co-stimulatory markers, and PD-L1) with an AUC of 0.72 for SVR followed by of 0.71 for CD86, Table 3. Using multivariate analysis exhibited that the decrease in PDL1 levels was significant ($p = 0.012$) and increase significant ($p = 0.024$) in CD86 associated with the response of treatment; Fig. 1.

Table 3
Diagnostic performances of significant markers to predict SVR.

Variables	AUC (95% CI)	P value	Cut-off	Sen	Spe	PPV	NPV	Accuracy
Fibro scan	0.63 (0.53–0.74)	0.03	13	52	59	93	11	53
AAR	0.68 (0.57–0.79)	0.003	1.12	63	63	90	15	63
PDL1	0.72 (0.61–0.83)	< 0.0001	0.6	68	56	94	15	67
CD40	0.62 (0.48–0.75)	0.05	0.7	57	56	91	11	57
CD83	0.64 (0.52–0.76)	0.02	0.32	59	60	91	12	57
CD86	0.71 (0.59–0.83)	< 0.0001	0.1	74	52	91	20	74
CD86 / PDL1	0.82 (0.75–0.94)	< 0.0001	1.0	78	74	91	20	77

Development Of Cd 86/ Pdl-1 Ratio For Svr

A ratio was developed named CD 86/ PDL-1 ratio = (CD 86/PDL-1) using stepwise regression model. The level of ratio was higher in non-responder than responder with significant difference ($p < 0.0001$). The median (IQR) of CD 86/PDL-1 in female and male were (2.3 (0.63–12.9); (0.23–23) respectively without significant differences ($p = 0.41$). Using best cutoff (≤ 1), CD 86/ PDL-1 ratio had a sensitivity of 78%, specificity of 74% and efficiency of 77% for SVR; Fig. 1.

CD 86/ PDL-1 ratio for predict SVR in dual and triple treatment

The levels of CD 86/ PDL-1 ratio in dual and triple treatment were presented in Fig. 2. The median levels of CD 86/ PDL-1 ratio were 4.1 (0.74–24.9) in responder patients vs. 0.53 (0.04–1.5) in non-responder in triple treatment. The median levels of CD 86/ PDL-1 ratio were 3.2 (0.65–18.0) in responder patients vs. 0.18 (0.01–0.68) in non-responder in dual treatment. Based on AUC, the CD 86/ PDL-1 ratio had the highest AUC for antiviral response in group 1, followed by the AUC of group 2.

Discussion

Predictors of response help treating doctors identify patients who are possible or impossible to reach SVR. Thus, these measures decrease the hazard of side effects and fees [20]. In the present study, we examined several biomarkers that are related to liver fibrosis formation and response to treatment. These variables are clinical variables or laboratory markers. Levels of routine laboratory tests such as liver enzymes were increased without significant difference in non-responder patients in comparison to responder patients. Levels of AAR significantly differed between non-responder patients and responder patients. These results agreed with Nachnani et al [21] concluded that on univariate analysis, AST/ALT ratio, INR, and occurrence of fatty liver were associated with non-response of Pegylated-IFN- α 2a plus Ribavirin. Patients with low HCV-RNA levels were associated with SVR compared with patients with high viral load [22]. Liver enzymes and synthetic functions tests had been described as indicators of prognostic markers for SVR. HOMA-IR index, insulin levels, viral load, glucose and liver histopathological, fatty liver score, and iron loading may have prognostic importance for SVR for Pegylated-IFN- α 2a plus Ribavirin [23]. DAAs are directed toward HCV-specific proteins and were added to PEG-IFN/RBV, leading to higher SVR that significantly increase SVR when added to PEG-IFN [24]. A triple combination of DAAs increases SVR rates and shortage time of HCV treatment weeks [25]. The indicators of DAA non-response in Egyptian CHC patients were older age, advanced liver fibrosis, and low thrombocytopenia [26]. In the present study, routine blood markers, liver fibrosis index, extracellular matrix markers, and dendritic cell markers) were evaluated, while in other studies few markers were evaluated. Model-for-end liver disease and ALT reduction during therapy were found to be reliable in predicting markers of DAA sustained-virological-response [27]. An SVR is related to a decrease in the fibrosis indicators, but the indicators do not reflect the disease activity during treatment. Baseline PIIINP was the only indicator for SVR [28]. Various studies have evaluated DC functions in chronic HCV. Our results exhibited that SVR patients exhibited higher levels of CD83, CD86, and CD40 and lower levels of PD-L1 in contrast to non-SVR

patients. Non-responders had higher C-X-C motif chemokine-10 in responders and lower NK cells level, higher level of NKp30, and lower level of the NK subset CD56- CD16+ [29]. Our results agree with the finding described by [30] who indicated that HLA-DR, CD40, CD83, and CD86 were lower in CHC patients. In the present study, the multivariate analysis of several indicators presented that the independent markers to predict SVR were PDL1 and CD 86. The highest levels of CD 86 and lowest levels of PDL1 were found in responders. These markers could be used to exclude non-SVR to treatment with dual and triple treatment. There was a positive correlation with PDL1 levels and a negative correlation inversely related to PD-L1/CD86 ratio [31]. The effect of PD-L1 confuses the effect of co-stimulatory markers [32, 33]. Future researches directions may also focus on large number of patients, multicenter study other markers for SVR. In conclusion, the present study demonstrated that the CD 86-PDL-1 ratio can be used as a predictor ratio for response to triple and dual DAA treatment of CHC patients.

Abbreviations

AAR
ALT/AST ratio
AFP
Alpha-fetoprotein
ALT
alanine aminotransferase
AST, aspartate aminotransferase
AUC
Area under curve
CHC
chronic hepatitis C
DAAs, direct-acting antiviral agents
DCs
Dendritic cells
HCV
hepatitis C virus
IQR
Interquartile range
LSM
liver stiffness measure
NK
nature killer
PDGF
platelet-derived growth
PD-L1
Programmed Cell Death Ligand 1

PEG INF + RBV
pegylated interferon and ribavirin
Pegylated interferon
PEG- INF
RT-PCR
reverse transcriptase polymerase chain reaction
SVR
Sustained virologic response
TE
transient elastography
TIMP-1
tissue inhibitor of metalloproteinase-1

Declarations

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Not applicable.

Authors' contributions

AMA, DO and MMO have equal contributions in designing the study. DO, MMO, AE were investigators who performed all clinical, laboratory investigations and data development. AMA and MMO were writing original draft preparation. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Cairo University Research Ethics committee (N-65-2014). An informed written consent was obtained from all participants.

Consent for publication

Informed consent was obtained from all subjects involved in the study.

Competing interests

The authors declare no conflict of interest.

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Figures

Figure 1

Caption not included with this version.

ROC of CD 86-PDL1 ratio for triple treatment

ROC of CD 86-PDL1 ratio for dual treatment

Figure 2

Caption not included with this version.