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RESEARCH ARTICLE

Efficacy of Direct-Acting Antiviral Combination Therapy in the Treatment of Hepatitis C Virus Among Kidney Transplant Patients

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ARTICLE HISTORY

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Abstract: ***Background*:** To date, there is no consensus on the best combination of direct-acting antivirals to treat hepatitis C virus in kidney transplant recipients.

***Objective*:** This study aims to analyze the efficacy of a combination of sofosbuvir and ledipasvir regimen for the treatment of hepatitis C virus infected kidney transplant patients.

***Method*:** A cross-sectional study was conducted in a nephrology clinic and the Nephrology Center in Basrah Teaching Hospital from June 2015 to June 2018. Ledifos (90 mg Ledipasvir and 400 mg Sofosbuvir fixed-dose) was given as a single daily dose to all the participants for 12 weeks. Response for therapy was tested by a follow up hepatitis C virus load at the end of 12 weeks and after 24 weeks. The sustained virological response was defined as a negative viral load of hepatitis C virus (aviremia) at the end of therapy. This study was done according to the Helsinki Congress.

***Results*:** A total of 60 (16 females) patients with renal transplantation and hepatitis C virus infection were included. The mean age was 40±6.2 years. A sustained virological response was observed in all of the patients who received Ledifos after 12 and 24 weeks of therapy for all genotypes (1a, 1b and 4); p= 0.0001. Genotype 1a was more prevalent among males, in about 34 (56.6%) of the patients; p= 0.0001, and it was the most common genotype that tested negative serologically, 11 (18.3%).

***Conclusion*:** Ledifos therapy is an effective and safe option for the treatment of hepatitis C virus infection in the post–renal transplant setting.

Keywords: Hepatitis C virus, kidney transplant, direct antiviral drug, genotype, ledipasvir, sofosbuvir, sustained virological response.

1. INTRODUCTION

Chronic hepatitis C virus (HCV) infection is an important health related issue. It includes six major genotypes (1 to 6). Some of which contain several subtypes referred to as a, b, c, etc. These subtypes have been recognized for clinical research. HCV is associated with serious problems in kidney transplant patients [1-4]. Many extrahepatic complications have been related to reduced kidney transplant longevity in HCV infected kidney transplants [5-7]. The persistent infection of HCV in kidney transplant patients, who are taking immunosuppressant drugs, has an immune-modulator effect that increases the risk of irreversible renal rejection and kidney allograft loss and hence, leads to low survival rate [3, 6, 8]. Furthermore, HCV infection is considered as a strong risk factor for transplant glomerulopathy, proteinuria, and new-onset diabetes [3, 8-10]. However, HCV infection should not prohibit kidney transplantation because the chances of survival of patients are better with kidney transplantation than on dialysis [8-10].

Several drugs have been used for the management of HCV infection in kidney transplants. Interferon-based therapy is not safe in kidney transplant setting due to the immunostimulatory properties of interferon, which can lead to an increased risk of acute rejection [2, 7]. In recent years, a number of new oral direct-acting antiviral (DAA) drugs against HCV were developed. The use of well-tolerated, efficient, and safe DAA is a crucial step in the treatment of HCV infection [10, 11]. Sofosbuvir, a NS5B nucleotide inhibitor, is used for HCV infection in patients with an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m2 [11]. Anti-HCV enzyme detected by immunoassays is usually positive in most of immunocompetent patients with detectable viral load. However, some patients such as those on dialysis, kidney transplant patients and those with acquired immunodeficiency syndrome may have false negative enzyme immunoassays serology [12, 13].

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A study of multiple dialysis centers in Germany conducted on 3000 haemodialysis patients revealed that 21.6 % of them were negative for HCV antibodies despite a positive viral load [14].

The goal of induction therapy is to prevent acute rejection during the early post transplantation period by providing a high degree of immunosuppression at the time of transplantation. Induction therapy is often considered essential to optimize outcomes, particularly in patients at high risk for poor short-term outcomes. All of the induction immunosuppressive agents currently used are biological and are either monoclonal (muromonab-CD3, daclizumab, basiliximab, alemtuzumab) or polyclonal (antithymocyte globulin [equine] or anti-thymocyte globulin [rabbit]) antibodies. Although anti-thymocyte globulin is not labeled for induction therapy, it is used for this purpose more than any other agent. Basiliximab is not considered a potent immunosuppressive agent but has a much more favorable adverse-effect profile compared with anti-thymocyte globulin and is most commonly used in patients at low risk for acute rejection [15, 16]. The combination of Sofosbuvir/ledipasvir has been used for genotypes 1, 4, 5, or 6 for a total of 12 weeks in the treatment of naïve patients. It is used for those without cirrhosis or with compensated cirrhosis for any detectable viral load of hepatitis C [17, 18].

Nevertheless, the data on the combination of choice for the treatment of HCV in kidney transplants is scarce.

This study aims to test the efficacy of a combination of sofosbuvir and ledipasvir in the treatment of HCV in kidney transplant patients and to study the prevalence of HCV genotypes and its subtypes in Iraqi kidney transplant patients and its correlation with viral loads.

2. MATERIALS AND METHOD

Participants were recruited at a nephrology clinic and the Nephrology Center in Basrah Teaching Hospital. Laboratory tests were done at the Middle East and Hayder al Rubai labs in Basrah. This was a cross-sectional study conducted from June 2015 to June 2018. A total of 80 participants were recruited in the study. Twenty of them were excluded because of missing data. Ultimately, 60 kidney transplant patients were included in the final assessment. The immunoassay serological tests were done for all patients by measuring the antibody of anti-hepatitis C virus by third-generation Enzyme Linked Immuno Assay (ELISA), (Biolisa HCV4.0 ELISA, Biokit Spain). All immunoassay serological antibody positive samples with or without high liver enzymes were tested for the HCV viral load by Real-time polymerase chain reaction (RT- PCR). The latter was done for the identification of HCV RNA. 100 µl of RNA was extracted from patient's sera using Quigen RNA extraction kit according to the kit protocol. Nested PCR was performed using the Taq DNA polymerase enzyme (Memmert Technologies, USA) in a volume of 20 µl reaction mix. The nested PCR products were visualized on 2% agarose gel under Ultraviolet light using (Uvitec gel documentation system). Alanine transaminase (ALT), plasma glucose, urea, and serum creatinine were performed by standard methods for all the participants. Hepatitis B surface antigen (HBsAg) and anti-hepatitis C antibodies (anti-HCV) were analyzed by ELISA. Hepatitis B infection positive and patients with kidney graft dysfunction with an estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73m^2 were excluded from the study. HCV viral load and genotypes were studied by the following materials: RT-PCR (Rotorgen 6000- Qiagen), Conventional PCR (Applied Biosystems 9700), Hybridization shaking water path (Memmert), Microplate spectrophotometer reader (ELX800 Biolisa reader biokit), Deep freeze (-40 Co), Refrigerator (2 - 8 Co), high speed centrifuge (0.5ml tube), centrifuge (10 -15 ml tube), different size micropipette (Eppendorf) 0.2,0.5,2,5,10 ml tube, Rack, powder free gloves, and PCR cabinet. A direct antiviral drug named Ledifos (manufactured by Indian brand company Hetero Healthcare Limited) was used. Ledifos is a combination tablet containing 90 mg Ledipasvir and 400 mg Sofosbuvir fixed-dose for once oral administration for 12 weeks. Response for therapy was tested by a follow up on HCV viral load at the end of 12 and 24 weeks. The sustained virological response (SVR) was defined as a negative viral load of HCV (aviremia) 12 and 24 weeks after completion of antiviral therapy. The safety of the tested drug was monitored by meticulous history taking and physical examination of the participants throughout the study period at each visit. In addition, blood tests for liver enzymes, bilirubin, and renal function were obtained from all the participants to monitor drug safety.

Analysis of data was done by using Statistical Packages for Social Sciences (SPSS 20). Pearson Chi square was used for the measurement of statistical significance among different variables. A p-value of less than 0.05 was considered significant.

3. RESULTS

This cross sectional study recruited 60 kidney transplant patients with hepatitis C viral infection; 44 males and 16 females. Age ranged from 14 to 60 years with a mean age of 40±6.2 years. The HCV viral load PCR ranges from 450 to 2000000 copies with a mean viral load of 1999550±567065 copies. The distribution of HCV genotype among kidney transplant patients in this study is shown in Fig. (**1**). Sustained virological response (SVR) after 12 and 24 weeks of therapy was observed in all of the patients irrespective of genotype. The most common genotype detected in males was genotype 1a, 34 (56.6%); p = 0.0001. However, in females, the distribution of all genotypes was equal (Table **1**).

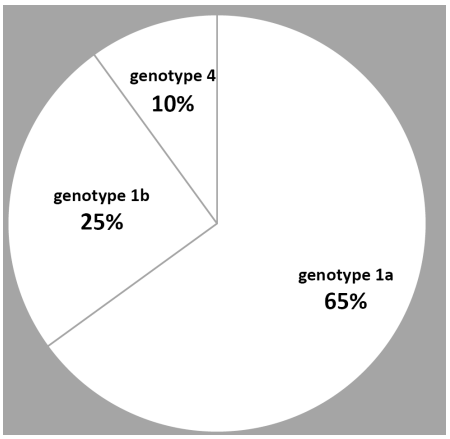

Fig. (1). Distribution of HCV genotype among studied patients.

Table 1. Distribution of HCV genotype according to gender.

Gender	Genotypes			Total
	1a	1b	4	
Female	5	5	6	16
Male	34	10	0	44
Total	39	15	6	60

Pearson Chi-Square = 20.66, p = 0.0001.

Similarly, genotype **1a** was the most commonly detected genotype among the age group (31-50 years), 31 (51.6%); p = 0.002 (Table **2**).

Table 2. Distribution of HCV genotype according to age.

Age Group (Years)	Genotypes			Total
	1a	1b	4	
10-30	6	5	5	16
31-50	31	10	0	41
51-60	2	0	1	3
Total	39	15	6	60

Pearson Chi-Square = 16.53, p =0.002.

Negative HCV serology was observed more in genotype 1a; 11 (18.3%); p = 0. 027 (Table **3**).

Table 3. Distribution of HCV genotype according to HCV serology status.

HCV Serology Status	Genotypes			Total
	1a	1b	4	
Negative HCV serology	11	0	0	11
Positive HCV serology	28	15	6	49
Total	39	15	6	60

Pearson Chi-Square = 7.25, p = 0.027.

The highest viral load was detected in genotype **1a**; 39 (65%) had a viral load ≥ 800 IU/L; p = 0.0001 (Table **4**).

Table 4. Distribution of HCV genotype according to HCV Viral load.

HCV Viral Load	Genotypes			Total
	1a	1b	4	
< 800 IU/L	0	5	0	5
≥ 800 IU/L	39	10	6	55
Total	39	15	6	60

Pearson Chi-Square = 16.36, p = 0.0001.

Cyclosporine based regimen was the most commonly used immunosuppressant regimen in genotype **1a**; 34 (56.6%); p = 0.0001 (Table **5**).

Table 5. Distribution of HCV genotype according to immunosuppressant regimens.

Immunosuppressant Regimens	Genotypes			Total
	1a	1b	4	
Tacrolimus based regimen	5	10	6	21
Cyclosporine based regimen	34	5	0	39
Total	39	15	6	60

Pearson Chi-Square = 26.18, p = 0.0001.

Anti-thymocyte globulin (ATG) induction was the most commonly observed induction regimen in genotype 1a during the peritransplant period; 36 (60%); p = 0.0001 (Table **6**).

Table 6. Distribution of HCV genotype among Induction therapy regimens in peritransplant period.

Induction Therapy	Genotypes			Total
	1a	1b	4	
Basiliximab induction	3	5	6	14
Anti-thymocyte globulin induction	36	10	0	46
Total	39	15	6	60

Pearson Chi-Square = 25.88, p = 0.0001.

Patients with diabetes mellitus were more likely to have genotype 1a; 21 (35%); p = 0.0001 (Table **7**).

Table 7. Distribution of HCV genotype according to diabetes mellitus status.

Diabetes mellitus	Genotypes			Total
	1a	1b	4	
No	18	15	6	39
Yes	21	0	0	21
Total	39	15	6	60

Pearson Chi-Square = 17.39, p = 0.0001.

Abnormal kidney graft function (increased blood urea and serum creatinine) was observed more in genotype 1a; 10 (16.6%); p value =0.0001 (Table **8**).

Table 8. Distribution of HCV genotype according to kidney graft function.

Renal indices	Genotypes			Total
	1a	1b	4	
Normal	29	15	6	50
Abnormal	10	0	0	10
Total	39	15	6	60

Pearson Chi-Square = 17.39, p = 0.0001.

Lastly, no documented side effects were observed from the use of the tested drug throughout the study period neither clinically nor biochemically.

4. DISCUSSION

This study recruited 60 kidney transplant patients with hepatitis C infection. A statistically significant association was found between genotype 1a with male gender and age group 31-50, 34. These results are consistent with other studies [19]. Similar to the other two studies, a statistically significant association was observed between negative HCV serology and genotype 1a [5, 14]. This can be explained by the suppressant effect of immunosuppressant drugs on antibodies in some patients with kidney transplantation. Seronegativity of genotype 1a was found in 18.3% of the cases, which makes HCV RNA viral load necessary for the diagnosis and follow up of patients infected with this genotype. Eradication of HCV infection after kidney transplantation seems to reduce the risk for HCV-associated renal dysfunction after transplantation and may reduce the risk for HCV disease progression. In this study, a SVR after 12 and 24 weeks of therapy in all of the patients irrespective of patient's genotype was documented. Several additional reports have described successful outcomes with combination DAA therapy in kidney transplants. Other studies found similar results [20, 21]. Sawinski *et al.* recruited 20 HCV-infected kidney transplant recipients (88% genotype 1a) who received sofosbuvir-based therapy with SVR at 12 weeks was 100% [22]. Treatment was well tolerated in this study without any discontinuations, dose reductions, graft rejections, or changes in serum creatinine levels. No drug-drug interactions with calcineurin inhibitors were observed.

ATG induction was the most commonly observed induction regimen in the perioperative period to prevent rejection. It was found that ATG causes more expression of HCV infection over the period of follow up of kidney transplant receipt. This was found more often in genotype 1a ;36 (60%); p = 0.0001 (Table **6**). Kidney graft dysfunction was not uncommon in this study. Infected patients with HCV may have higher blood urea and serum creatinine (which are attributed to neither rejection nor other medical causes). This was observed more in genotype 1a, in about 10 patients (16.6%); p = 0.0001 (Table **8**). The combination sofosbuvir/ledipasvir (Ledifos) was evaluated for safety in many trials and found to be relatively safe with minor side effects such as headache, insomnia, and nausea [17, 18]. However, in this study, no side effects were reported throughout the study period.

CONCLUSION

HCV genotype 1a is the most common genotype in kidney transplant patients in this study. HCV RNA viral load should be implemented for the diagnosis and follow up of patients with hepatitis C infection in post-transplant period. Sofosbuvir and Ledipasvir combination therapy is an effective and safe option for the treatment of HCV infection in the post-renal transplant setting. Using ATG induction is a potential risk for hepatitis C infection. The vigilance of nephrologist and transplant surgeon is required in pre and post-transplant period to discover HCV infections through a review of risk factors and observation of liver enzymes.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethical Committee of the College of Medicine, University of Basrah.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

HUMAN AND ANIMAL RIGHTS

This study was approved by the Ethical Committee of the College of Medicine, University of Basrah. The legal and ethical approval was obtained prior to the initiation of the research work.

CONSENT FOR PUBLICATION

Informed consent was obtained from all patients for being included in the study.

AVAILABILITY OF DATA AND MATERIALS

Not Applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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