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The Efficacy and Safety of Treatment of Chronic HCV Infection by Ombitasvir/Paritaprevir/Ritonavir with Ribavirin and its Effect on Complement C3 and C4 Levels

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Abstract

Background: Chronic hepatitis C virus (HCV) infection is a major health risk worldwide. The complications do not only involve the liver but extend to several extrahepatic areas due to its immunological effects on B cells and the complement system. Since 2014, directly acting antiretroviral drugs (DAAs) have revolutionized the way we treat HCV infection.

Aim of Study: To determine whether treating patients with chronic HCV infection with combination of Ombitasvir / Paritaprevir / Ritonavir (OBV/PTV/r) and Ribavirin (RBV) is effective and determine its effect on serum complement (C) levels.

Patients and Methods: Fifty patients with chronic HCV infection (Child-Pugh A) naïve to DAA treatment were included in this study; all patients received two tablets orally daily of OBV/PTV/r. Each tablet contains 12.5mg ombitasvir, 75mg paritaprevir, 50 mg ritonavir in addition to RBV 1000-1200mg one tablet daily all for 12 weeks. Patients were followed-up monthly for 3 months, for side effects and laboratory tests. Laboratory measurements included HCV PCR at baseline and 24 weeks, alpha fetoprotein (AFP), C3, C4 levels at start of treatment and after 6 months. Liver function tests; alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin and albumin, besides international normalization ratio (INR), complete blood count (CBC) and serum creatinine were repeated at 4, 8,12 and 24 weeks from start of treatment.

Results: All patients achieved sustained virological response at 24 weeks (SVR24) with minimal complications. There was a statistically significant increase in serum C3 and C4 levels (1.05g/L ± 0.29 to 1.26 g/L ± 0.27 and 0.24g/L ± 0.09 to 0.32g/L ± 0.07, respectively). There was a significant decline is ALT and AST levels (64.76U/L ± 34.82 to 25.58U/L ± 8.24 and 61.94U/L ± 25.73 to 23.3U/L ± 8.36, respectively); and although hemoglobin levels declined by end of treatment no patient required stopping medication or blood transfusion.

Conclusion: Treatment of HCV infection by combination of OBV/PTV/r with RBV is effective and safe in eradicating chronic HCV infection. Successful treatment of HCV improves complement C3 and C4 levels in those patients.

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Key Words: *Hepatitis C – Directly acting antiretrovirals – Complement levels.*

Introduction

HEPATITIS C virus infection affects approximately 3% of the world's population with an estimated 170 million people worldwide infected. About 70% of those affected establish a chronic infection [1]. Chronic HCV infection leads to a myriad of complications including liver fibrosis, cirrhosis and hepatocellular carcinoma [2]. These complications account for approximately 700,000 deaths annually [3]. Egypt, being among the top countries carrying the heavier burden of infection, has started a program of mass HCV treatment since 2007 which started with pegylated interferon (IFN) and ribavirin then later with directly acting antiretroviral agents (DAAs) [2].

In addition to its deleterious effects on the liver, HCV infection can cause a variety of extrahepatic manifestations through its interaction with the immune system. Through different strategies, HCV is able to evade innate and adaptive antiviral responses of the host immune system in-order to establish a chronic infection. One of those strategies involves inhibiting the complement (C) system components either directly or indirectly by inducing complement inhibitors [4].

The complement system comprises of a set of more than 30 soluble and membrane bound proteins, its primary goal is assisting the immune system in clearing out pathogens through the classical, alternative and lectin pathways ending with the formation of the membrane attacking complex (MAC) leading to cellular responses like apoptosis,

opsonization and the amplification of inflammatory reaction [5]. It was established that HCV can inhibit C3 convertase activity, an enzyme that is critical in promoting the activity of the classical and lectin pathways [6]. In addition, an in vitro study reported that C3 promotor activity was inhibited in hepatocytes infected with HCV [7]. Moreover, when serum and liver biopsy samples from HCV patients compared to those obtained from serum and tissue of healthy donors, both the levels of C3 in serum and the expression of mRNA in biopsies were lower in HCV infected patients [7].

Complement dysregulation can lead to autoimmune conditions, in particular for HCV, type II mixed cryoglobulinemia (MC) and B cell lymphoma [8]. Clearance of HCV may help in improving complement levels as evidenced in several studies that showed higher serum C3 and C4 complement levels in patients after treatment with pegylated IFN and ribavirin [9,10,11]. Moreover, higher C3 and C4 serum concentrations correlated positively with good response at the end of IFN and ribavirin treatment [9,11]. A single arm pilot clinical trial by Sise et al., [12] in 2020 examined the effect of ledipasvir 90mg/sofosbuvir 400 mg once daily for patients with HCV genotype 1 or 4 infection and chronic kidney disease (CKD). Complement levels were followed-up during treatment. There was a significant rise in both levels of C3 and C4. The rise in C4 was associated with improvement of the estimated glomerular filtration rate (GFR) and proteinuria [12].

In recent years, options for treating hepatitis C virus have advanced rapidly [13]. Interferon free regimens with oral DAAs are the standard of care as they are associated with higher rates of sustained virological response (SVR) [14]. The first regimen to contain three distinct DAAs approved for treating HCV patients who are both treatment naive and treatment experienced, is the combination of the NS5A inhibitor ombitasvir (OBV), the NS3/4A non-structural protein inhibitor paritaprevir (PTV) and ritonavir (*r*) with or without ribavirin (RBV) [15]. Although this regimen is highly effective in clearing out the virus, it is currently not recommended for patients with Child-Pugh B liver disease due to reports of hepatic decompensation in those patients [16].

The aim of this study is to determine whether clearance of HCV by DAAs namely OBV/PTV/r +RBV has an effect on serum complement levels in HCV infected patients who have complement levels within normal range.

Patients and Methods

The present prospective cohort study was conducted on fifty adult HCV-genotype 4 infected patients naïve to treatment with DAAs at Nasser Institute for Research and Treatment (Cairo, Egypt) from May to December 2019.

Eligible patients were started on a 12-week course of combination therapy of oral OBV/PTV/r 12.5mg/75mg/50mg two tablets taken once daily with a total daily oral dose of 1000 or 1200mg RBV (weight-based); 1000mg if the patient's body weight was less than 75kg or 1200mg if 75kg and they were followed-up for 12 weeks after completion of treatment.

Inclusion criteria: (I) HCV PCR positive patients, (II) above 18 years of age, (III) Child Pugh A liver disease.

Exclusion criteria: (I) Child-Pugh B-C, (II) HBV or HIV infection (III) active infection and active malignancy. (IV) previous IFN or DAAs therapy, (V) patients with any history of autoimmune diseases.

The diagnosis of HCV was based on the presence of a viral load >50IU/ml assessed by HCV-PCR. Relapse was defined as detectable HCV RNA after having an undetectable RNA following the end of treatment. SVR: The HCV is not detected in the blood 12 weeks or more after completing treatment.

Approvals and ethical considerations:

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and was approved by the Research Ethics Committee for experimental and clinical studies at the Faculty of Pharmacy Cairo University (REC-FOPCU; PT: 2405) and National Committee for Control of Viral Hepatitis of Ministry of Health and Population, Egypt. This study was registered in clinical trial.gov. All patients enrolled in this study gave their written informed consent to the data collection and the conduction of the study.

Laboratory measurements:

Assessment of serum HCV mRNA by qRT PCR. HCV mRNA was quantified in the serum by the Cobas Ampli Prep/Cobas TaqMan HCV-RNA assay v 2.0 (Roche Molecular Diagnostics, CA, USA) with a lower detection limit at 15IU/ml.

Assessment of liver function and INR. Alanine transaminase (ALT), aspartate transaminase (AST), albumin, total bilirubin and the international normalization ratio (INR) were done routinely.

Assessment of serum C3 and C4. Detection of C3 and C4 were performed in sera by nephelometry immunoassay analyzer.

Hepatitis B virus surface antigen (HBsAg) was tested using an ELISA kit purchased from Abbott Laboratories (IL, USA, version 3) whereas the HIV level was detected using the Sinosource Biopharmaceutical (Sichuan, China) ELISA kit.

Serum alpha fetoprotein (AFP) level. The assessment was done using Architect 2000 system (ABBOTT Diagnostics, TX, USA) according to the manufacturer's transcript.

Hematological tests: Complete blood picture (CBC) was done using an automated hematology analyzer cell dyne-1800 (Abbott Diagnostics, IL, USA) and the Hb level was also determined.

Assessment of outcomes:

The primary outcome was the clearance of HCV from blood after 24 weeks (SVR 24) with the DAA antiviral combination therapy together with monitoring improvement in serum C3 and C4 levels for the assessments of immunological recovery, whereas monitoring the complications in the form of hepatic decompensation, anemia and other hematological changes (white blood cell (WBC) and platelets count, renal dysfunction(serum creatinine) that may develop during treatment were the secondary endpoints.

All patients in our study were subjected to the following: Full history, full clinical examination and laboratory investigations before treatment. Regular follow-up monthly visits at control unit of viral hepatitis of Nasser Institute for Research and Treatment. During these visits side effects if present were registered and in between monthly visits by telephone or extra visits if needed.

Baseline values were obtained on the first day before starting the treatment regimen; and the normal reference ranges are as follows: ALT (0-34U/L); AST (7-40U/L); albumin (3.2-4.8g/dl); total bilirubin (0.3-1.2 mg/dl); INR (0.9-1.27); C3 (0.9-1.8g/L); C4 (0.1-0.4g/L); Hb (11.5-15.5g/dl); WBC (4.5-11.0 $x10^9$/L); platelets (150-450 $x10^9$/L); sCr (0.5-1.1mg/dl).

Statistical analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 25). Data was presented and suitable analysis was done according to the type of data obtained for each parameter; p-value < 0.001 p-value <0.005 was considered statistically significant (S) whereas p-value >0.05 is non-significant (NS).

i- *Descriptive statistics:*

1- Mean, standard deviation (± SD) and range for parametric numerical data, while median and interquartile range (IQR) for non-parametric numerical data.
2- Frequency & percentage of non-numerical data.

ii- *Analytical statistics:*

1- Repeated measure ANOVA test was used to assess the statistical significance of the difference between more than two study group means.
2- Post Hoc Test is used for comparisons of all possible pairs of group means.
3- Paired *t*-test was used to assess the statistical significance of the difference between two means measured twice for the same study group.

iii- *Correlation analysis:*

Pearson correlation analysis was used for parametric variables, whereas Spearman correlation analysis was used for non-parametric data.

Results

Patients characteristics:

This study included 50 patients, the mean age for the study population was 47.2±4.8 yrs, the majority were males (n=31) and 19 females. The mean BMI was 25.1±1.9kg/m^2. Thirty patients had other co-morbidities in addition to HCV infection, hypertension (n=10), diabetes mellitus (n=9) and ischemic heart disease (n=4).

Effectiveness:

All patients had a positive HCV PCR at start of the study with mean value 607.5±347.5 copies/ml at baseline. At 24 weeks, all patients (n=50) had a negative PCR (<15 viral copies/ml).

Safety:

All patients continued the study and the course of treatment with no major complications. Thirty percent of the patients reported mild symptoms namely fatigue, nausea and abdominal discomfort but continued to be compliant on treatment.

Laboratory parameters progression over the course of treatment is given in Table (1). There was a significant decline in liver enzymes (AST, ALT) from baseline to week 24 which was consistent during the follow-up period; ALT levels (64.76U/L ± 34.82 to 25.58U/L ± 8.24; p-value <0.001) and AST levels (61.94U/L ± 25.73 to 23.3 U/L ± 8.36l; p-value <0.001).

Table (1): Laboratory parameters progression over the course of treatment.

	Baseline Mean ± SD	Week 4 Mean ± SD	Week 8 Mean ± SD	Week 12 Mean ± SD	Week 24 Mean ± SD	Repeated measure ANOVA		
						F	*p*-value	Sig.
ALT (IU/L)	64.76±34.82	40.64±15.36	34.98±14.9	28.4±10.44	25.58±8.24	74.956	<0.001(A1)	S
AST (IU/L)	61.94±25.73	41.68±15.94	35.06±13.22	28.8±9.13	23.3±8.36	119.84	<0.001(A1)	S
Albumin (g/dl)	3.83±0.48	3.8±0.28	3.78±0.32	3.8±0.3	3.87±0.21	1.368	0.260	NS
Total bilirubin (mg/dl)	1.09±0.21	1.38±0.19	1.24±0.17	1.13±0.16	1.12±0.13	45.921	<0.001(A2)	S
INR	1.17±0.06	1.22±0.07	1.19±0.06	1.19±0.04	1.17±0.04	7.120	0.001(A3)	S
Creatinine (mg/dl)	0.95±0.17	0.91±0.13	0.89±0.12	0.86±0.1	0.85±0.08	8.924	<0.001(A4)	S
Hemoglobin (g/dl)	14.01±1.13	12.61±1.36	12.36±1.07	12.26± 1.03	12.9±0.91	47.866	<0.001(A5)	S
Platelets	278.02±48.53	279.98±42.71	287.34±41.2	288.9±40.93	326.8±58.91	23.931	<0.001(A6)	S
White blood. Cell count	5.37±0.99	5.67±1.13	5.37±0.71	5.24± 1.04	5.41±1.53	1.168	0.324	NS

Hemoglobin levels decreased significantly (*p*-value <0.001) from baseline levels (mean = 14.01 g/dl ± 1.13) to week 24 levels (mean = 12.9g/dl ± 0.91) and this decline has been consistent through week 4,8 and 12; however, no patient required blood transfusion.

There was a statistically significant decline in serum creatinine (mean = 0.95g/dl ± 0.17 at baseline vs 0.85g/dl ± 0.1 at week 24.

Serum AFP mean levels declined from 7.44ng/ml ± 6.72 at start if treatment to 6.44ng/ml ± 3.12 at the end of 24 weeks which was not found to be statistically significant Table (2).

Serum C3 and C4 levels:

Mean serum C3 levels at baseline were 1.05g/L ± 0.29, these levels increased towards the end of treatment and by week 24 mean to reach 1.26g/L ± 0.27 which was found to be statistically significant Table (2) & Fig. (1). Same findings for C4 which started treatment with a mean of 0.24g/L ± 0.09 and increased to 0.32g/L ± 0.07 which was found to be statistically significant (*p*-value <0.001; Table (2) & Fig. (2).

Table (2): AFP, C3 and C4 levels before and after treatment at 24 weeks.

	Baseline Mean ± SD	24 Mean ± SD	Paired *t*-test		
			t	*p*-value	Sig.
AFP	7.44±6.72	6.44±3.12	1.367	0.178	NS
C3	1.05±0.29	1.26±0.27	–4.154	<0.001	S
C4	0.24±0.09	0.32±0.07	–4.751	<0.001	S

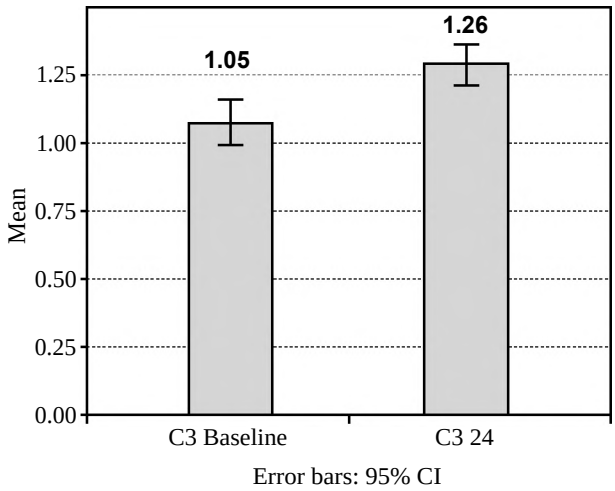

Fig. (1): Changes in C3 levels before and after HCV treatment at 24 weeks.

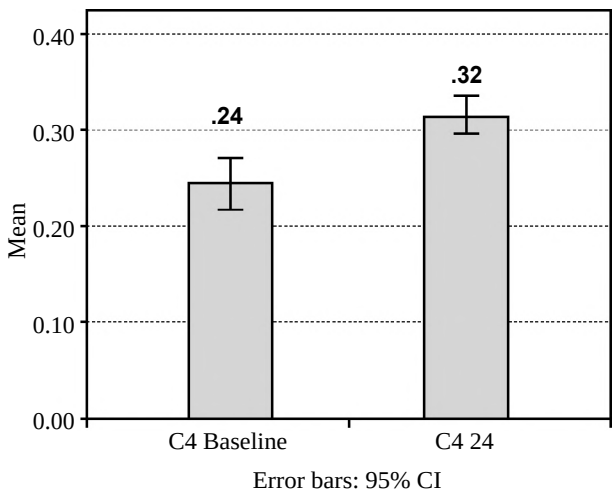

Fig. (2): Changes in C4 before and after treatment at 24 weeks.

Correlation analysis:

Table (3) shows that when comparing levels of C3 and C4 to viral load before the start of treatment there was a significant correlation with lower C3 levels and higher viral loads Fig. (3). Although lower C4 levels were associated with higher viral load, this was not found to be statistically significant.

Table (3): Correlation between HCVRNA and C3&C4 at baseline.

	C3 baseline	C4 baseline
HCVRNA:		
Spearman's rho	–0.565	–0.258
p-value	<0.001	0.070
Significance	S	NS

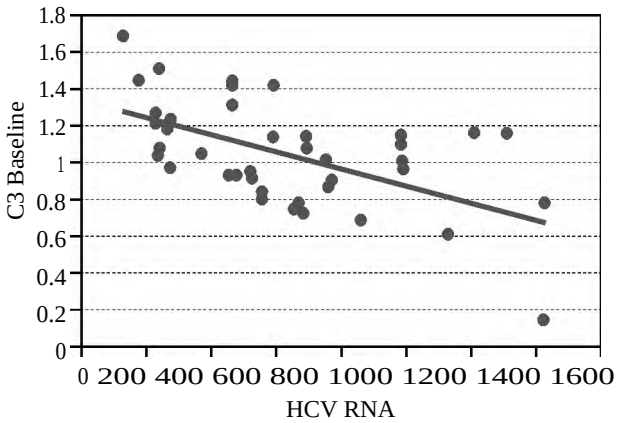

Fig. (3): Correlation between HCV RNA level and C3 at start of treatment.

Moreover, as depicted from Tables (4,5), patients with higher serum creatinine had lower complement levels this was only statistically significant in the case of C3 with a *p*-value of 0.005 Fig. (4). This finding was also significant at 24 weeks Fig. (5).

There was no significant correlation between ALT levels and complement levels at start of treatment and after 24 weeks.

Table (4): Correlation between creatinine and C3&C4 at baseline.

	C3 baseline	C4 baseline
Cr baseline:		
Pearson Correlation	–0.392	–0.209
p-value	0.005	0.145
Significance	S	NS

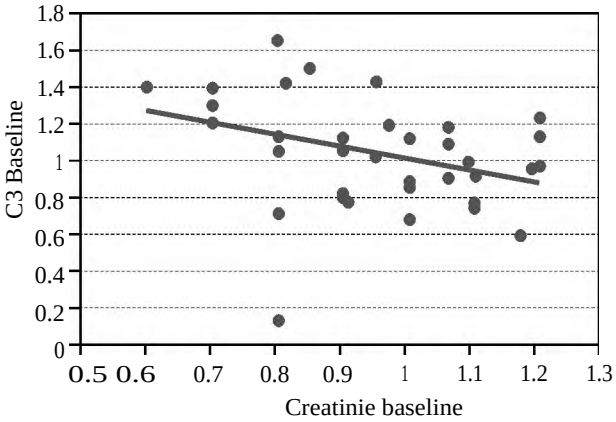

Fig. (4): Correlation between serum creatinine and C3 at start of treatment.

Table (5): Correlation between creatinine and C3&C4 at week 24.

	C3 24	C4 24
Cr 24:		
Spearman's rho	–0.413	–0.112
p-value	0.003	0.440
Significance	S	NS

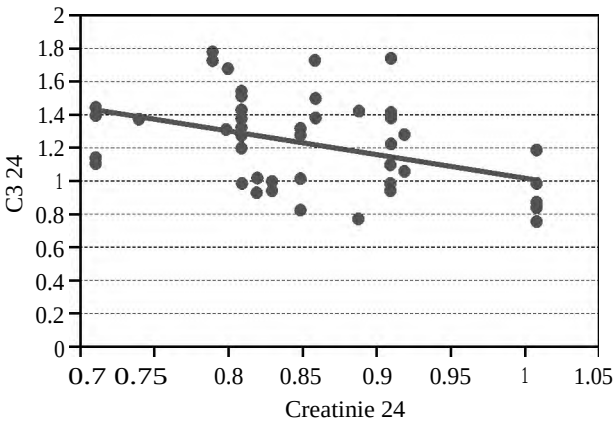

Fig. (5): Correlation between serum creatinine levels and C 3 levels after 24 weeks.

Discussion

Combination of OBV/PTV/r with RBV is not usually the first choice of DAA for treatment of HCV in patients with normal renal functions due to its effects on Hb levels when combined with ribavirin [17] and reports of hepatic decompensation in Child-Pugh B patients [16]. It is usually reserved for those with chronic kidney disease due to its primarily hepatic elimination.

The objective of this study was to determine whether the combination of OBV/PTV/r with RBV is effective at clearing HCV infection safely and

whether clearing out HCV infection can cause recovery from HCV immunological effects namely its effect on the complement system.

When DAAs were introduced they offered for the first time in the fight against chronic HCV infection a possibility of achieving SVR over 90% [18]. DAAs have raised hopes of being an effective treatment against HCV extrahepatic manifestations such as mixed cryoglobulinemia.

We have observed a 100% SVR at week 12 (SVR12) and week 24 (SVR 24) in our study population treated for HCV. In the AMBER study, 99% of the patients achieved SVR12 when treated with OBV/PTV/r with RBV; however, in that study dasabuvir was added to the treatment regimen for patients with genotype 1 [17]. The majority of HCV infection in Egyptian population is genotype 4.

Alanine transaminase (ALT) levels are a biochemical marker for hepatocytolysis induced by HCV infection [18]. As expected, ALT levels decreased significantly after eradication of HCV infection and during the course of treatment. It was observed that ALT levels started to normalize by week 8. A study by Trifan et al., [19] tested SVR after 8 weeks and 12 weeks treatment with OBV/PTV/r and the results were comparable at SVR12 rates were 97.7% in the 8-week treatment group and 96.4% in the 12-week treatment group [19] which may suggest a shorter course of treatment might be equally beneficial but more studies are required to validate this point.

There was a significant drop in Hb levels in our study group from start of treatment till week 12 and although it was statistically significant none of our patients required blood transfusion or iron treatment and ribavirin was not discontinued.

The labels for OBV/PTV/r + DSV recommend co-administration of RBV for patients with genotype 1a and genotype 4 infection [20]. The RUBY-I Cohorts results showed that only patients who received RBV had Hb levels <8g/dl. RBV needed to be discontinued or dose modified in weeks 4 and 5 [21]. This was consistent with previous analysis that showed considerable decrease in Hb within the first 2 to 4 weeks of initiating treatment with RBV [22].

However, the results of the PEARL-IV study which studied genotype 1 a-infected patients who received OBV/PTV/r + DSV, SVR rates were 90% in those who received a RBV-free regimen and 97% in those who received RBV [23]. In addition, the RUBY-II, a RBV-free regimen (OBV/PTV/r ± DSV) was studied in 18 patients with genotype 1a or 4. A high SVR12 rate was observed (94%) with no episodes of anemia [21]. It is currently recommended to lower the initial dose of RBV in patients with renal insufficiency, further dose modification is recommended when Hb drops during the course of treatment; however, adherence to these recommendations did not eliminate the risk of anemia in patients using RBV [21].

HCV infection is a systemic illness giving rise to several extra-hepatic manifestations. The kidneys appear to be an important target [24]. HCV can give glomerular and tubulointerstitial damage through activation and deposition of cryoglobulins and immune complexes respectively [25]. Additionally, oxidative stress and pro-inflammatory cytokines help the development of renal disease by vascular injury [26].

Serum creatinine levels declined during the study period; however, all patients involved in the study had creatinine levels within normal range, it was observed that at baseline results, lower C3 levels were correlated significantly with higher serum creatinine levels. However, body weight and co-morbidities should have been taken into consideration when considering this correlation.

Viral load (HCV RNA copies per ml) correlated significantly with lower C3 levels and was associated with lower C4 levels too; consequently those levels increased at week 24 after eradication of viral load. Complement levels have been suggested as a marker for response to DAA treatment with an increasing level of complement from baseline in those who respond to antiviral treatment. Since our study had 100% SVR we could not validate this point against non-responders.

In a study in 2014, serum levels of C3 and C4 were found to be significantly reduced in all patients with chronic HCV infection [11]. Both C3 and C4 had significantly increased in responders to IFN when compared to non-responder after treatment. In fact, the higher C3 and C4 in the serum the more this correlated with a good end-of-treatment response in patients treated with IFN and RBV [11]. This is in agreement with the findings in our study, consolidating the same findings but using OBV/PTV/r and RBV regimen, which proved effective at increasing serum complement levels. Further studies are needed to verify the effect of these findings on patients with renal impairment and its effect on their level of proteinuria.

Conclusion:

HCV infection not only affects the hepatocytes but also has an effect on the immune system in the form of complement inhibition, HCV infected patients have lower complement levels than the normal population. Improving C3 and C4 levels can be used as a marker for eradication of HCV infection after DAA treatment. Treatment with a combination of OBV/PTV/r and RBV was safe and effective in maintaining SVR six months post treatment in our study population.

Ethical considerations: The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and was approved by the Research Ethics Committee for experimental and clinical studies at faculty of Pharmacy Cairo University (REC-FOPCU; PT: 2405) and National Committee for Control of Viral Hepatitis of Ministry of Health and Population, Egypt. This study was registered in clinical trial.gov. All patients enrolled in this study gave their written informed consent to the data collection and the conduction of the study.

Consent for publication: Written and informed consent was taken from all the study participants

Availability of data and material: Data are available upon request.

Competing interests: The authors declare that there is no conflict of interest.

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Author contributions: Conceptualization, LK, MA, DA and HA; supervision, LK, DA and HA; analysis and verified data verification, DA and HA; data collection and patients followed-up, MA; hands-on experiments, MA; LK wrote the manuscript; all authors revised the manuscript.

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فعالية وسلامة معالجة عدوى فيروس إلتهاب الكبد الوبائى سى (HCV) المزمن بواسطة أو مبيتاسفير (Ombitasvir)/باريتابريفير (Paritaprevir)/ريبافيرين (Ribavirin) مع ريبافيرين (Ribavirin) وتأثيره على مستويات C3 و C4 التكميلية

مقدمة: تعد عدوى فيروس إلتهاب الكبد الوبائى سى (HCV) من المخاطر الصحية الرئيسية فى جميع أنحاء العالم. المضاعفات لا تشمل فقط الكبد ولكنها تمتد إلى عدة مناطق خارج الكبد بسبب آثارها المناعية.

الهدف من الدراسة: تحديد ما إذا كان علاج المرضى المصابين بعدوى إلتهاب الكبد C المزمن باستخدام مزيج من أو مبيتاسفير/باريتابريفير/ريبافيرين [Ombitasvir/Paritaprevir/Ritonavir (OBV/PTV/r)] وريبافيرين [Ribnvirin (RBV)] فعالاً وتحديد تأثيره على مستويات (C3,C4).

تم ادراج خمسين مريضاً مصاباً بعدوى إلتهاب الكبد الوبائى المزمن HCV للعلاج فى هذه الدراسة. تلقى جميع المرضى قرصين عن طريق الفم يومياً يحتوى كل قرص على ١٢.٥ مجم أومبيتاسفير، ٧٥ مجم باريتابريفير، ٥٠ مجم ريتونافير بالإضافة إلى ريبافيرين ١٢٠٠–١٠٠٠ مجم قرص واحد يومياً لمدة ١٢ أسبوعاً. تمت متابعة المرضى شهرياً من أجل الآثار الجانبية والاختبارات المعملية. تضمنت القياسات المختبرية المأخوذة HCV PCR فى الأساس و ٢٤ أسبو عاً، ومستويات ألفا فيتوبروتين (AFP)، ومستويات C3، و C4 فى بداسة العلاج وبعد ٦ أشهر. وتمت اختبارات وظائف الكبد، تم تكرار (ALT)، (AST)، وإجمالى البيليروبين والألبومين، إلى جانب (INR)، وتعداد الدم الكامل (CBC) والكرياتينين فى الدم فى ٤ و ٨، ١٢ و ٢٤ أسبو عاً من بدء العلاج.

النتائج: حقق جميع المرضى استجابة فيروسية مستدامة فى الأسبوع ٢٤ (SVR24) مع الحد الأدنى من المضاعفات. كانت هناك زيادة ذات دلالة إحصائية فى مستويات C3 و C4 و فى الدم. كان هناك إنخفاض كبير فى مستويات ALT و AST. وعلى الرغم من إنخفاض مستويات الهيموجلوبين بنهاية العلاج، لم يحتاج أى مريض التوقف عن تناول الأدوية أو نقل الدم.

الخلاصة: إن علاج عدوى إلتهاب الكبد C عن طريق الجمع بين OBV/PTV/r مع هو علاج فعال وآمن فى القضاء على عدوى HCV المزمنة. العلاج الناجح لفيروس إلتهاب الكبد سى يحسن مستويات C3 و C4 التكميلية لدى هؤلاء المرضى.