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Effect of Treatment of Ombitasvir with Paritaprevir/Ritonavir plus Ribavirin on Naïve Patients with Chronic Hepatitis C Virus Genotype 4

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Abstract

Direct-acting antivirals (DAAs) combination therapies from various mechanisms of action and families have been revolutionized the management landscape of chronic hepatitis C virus (HCV). Ombitasvir, paritaprevir with ritonavir (OBV/PTV/r) ± ribavirin (RBV) is approved to treat HCV genotype 4 (GT4) infections. Here, our objective was to delineate the efficacy and safety of OBV/PTV/r plus RBV in treating of Egyptian naive patients infected with HCV GT4.

A cohort of 100 Egyptian patients infected with HCV GT4 was allocated and administered orally OBV/PTV/r with RBV. The primary endpoint of our study was a sustained virological response (HCV RNA < 12 IU/mL) 12 weeks after the cessation of the treatment (SVR12). This study is registered with ClinicalTrials.gov, number NCT04378608.

Among treatment naive patients with OBV/PTV/r+ RBV, SVR12 rates achieved 97% (97/100) in overall patients. Regarding treatment failure, the regimen recorded 3 % had treatment failure (0 null-responses, 3 relapses). However, the most frequently common adverse events recorded were a headache (28%), fatigue (18%), asthenia (23%), nausea (19%) and dyspnea (14%).

The interferon-free regimen combination of OBV/PTV/r plus RBV achieved excellent SVR12 rates, 97%, with virologic outcome failures 3%, and it was generally safe and well tolerated for treating naïve patients infected with HCV GT4.

Keywords Egyptian naïve, HCV, genotype 4, IL-28β, Ombitasvir, Paritaprevir, Ritonavir, Ribavirin. Abbreviations used.

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تأثير علاج أومبيتاسفير مع ريبافيرين وباريتابرفير/ ريتونافير على المرضى الغير معالجين و المصابين بالتهاب الكبد الفيروسى المزمن من النوع سى والنمط الجيني ٤

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الخلاصة

لقد أحدثت العلاجات بمضادات الفيروسات ذات المفعول المباشر (DAAs) ثورة في مشهد استئصال فيروس التهاب الكبد الوبائي المزمن . (HCV)

لقد تمت الموافقة على استخدام (OBV / PTV / r/RBV) لعلاج . HCV (GT4)

كان هدفنا هنا هو تحديد فعالية وسلامة OBV / PTV / r plus RBV في علاج المرضى المصريين المصابين بفيروس.HCV GT4

تم تخصيص مجموعة من ١٠٠ مريض مصري مصاب بفيروس HCV GT4 وإعطائهم عن طريق الفم هذا العلاج. تعتبر النتيجة ايجابية (HCV RNA <12 IU / mL)بعد ١٢ أسبوعًا من توقف العلاج .

هذه الدراسة مسجلة في ClinicalTrials.gov برقم.NCT04378608 , وقد حققت معدلات SVR12 معدل ٩٧ % (١٠٠/٩٧) في إجمالي المرضى. فيما يتعلق بفشل العلاج، سجل النظام ٣ ٪ فشل العلاج. ومع ذلك ، كانت الاعراض الجانبية الأكثر شيوعًا المسجلة هي الصداع (٢٨٪) ، والتعب (١٨٪) ، والوهن (٢٣٪) ، والغثيان (١٩٪) وضيق التنفس (١٤٪) ، وبذلك يمكن ان نستنتج ان نظام العلاج الخالي من الإنترفيرون من OBV / PTV / r plus RBVمعدلات ممتازة لـSVR12 ، ٩٧٪ ، مع فشل فيروسي بنسبة ٣٪ ، وكان العلاج بشكل عام آمنًا وجيد لعلاج المرضى المصابين بفيروسHCV GT4 .

الكلمات المفتاحية : المرضى المصريين، التهاب الكبد الفيروسى سى، النمط الجينى ٤، انترلوكيين ٢٨ ب، أومبيتاسفير، ريبافيرين، باريتابرفير/ ريتونافير

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Introduction

Hepatitis C virus (HCV) infection affects an estimated 71.1 million people have chronic hepatitis C infection worldwide, is considered the major cause of hepatic morbidity and mortality [1,2]. Moreover, HCV genotype 4 (GT4) accounts for the prevalence of most HCV infections in areas of the Middle East, North Africa, and sub-Saharan Africa, and in some European countries [3]. Moreover, it has a prevalence up to 20 %, and more than 90% in Egypt with subtype 4a predominate [4].

Importantly, there has been a revolution in the curing of chronic HCV whereby a few different direct-acting antivirals (DAAs) combination from of action and families have run into advanced to heighten virological outcome, minimize the side effects, devalued the risk of resistance, and reduce the time of the therapy [5]. With the emergence of excellent efficacious HCV DAAs regimen options, the Egyptian National Committee for Control of Viral Hepatitis began recruiting patients for treatment in September 2014 and by the end of 2017, about 1.5 million Egyptians was enrolled for treatment purpose [6].

The combination therapy of ombitasvir (OBV), paritaprevir (PTV), and ritonavir (r) (OBV/PTV/r) has been approved [7], and each of these combined regimens is largely metabolized in the liver, with lower renal clearance; as such, this regimen is not contraindicated in treatment of chronic renal failure patients [7]. However, OBT/PTV/r regimen is preferred for patients with creatinine clearance less than 30 mL/min. [8]. Going ahead, the standard of care for chronic HCV patients is a combination of two to four DAAs [9]. Thus, a fixed-dose tablet comprising OBV/PTV/r plus ribavirin (RBV) is a valuable for the treatment of chronic HCV GT4 infection [10]. Ritonavir (a CYP3A inhibitor) is added to boost PTV exposure [11], and this combined regimen is considered one of the recommended options for the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines for treatment-naive and experienced patients infected with chronic HCV GT4 [12].

The IL-28B gene, which is located on chromosome 19q, was discovered in 2003 [13]. IL-28B gene polymorphism is considered as a strong predictor of SVR [14]. Patients who have the IL28B CC genotype are more likely to respond to peg-IFN and RBV treatment, whereas patients who have the TT genotype are more likely to be non-responders [15].

Previous clinical trials indicated that the OBV/PTV/r combined therapy had highly efficacious in different scenarios, such as treatment of genotype1a, 1b and 4 chronic HCV as well as in treating naive, experienced, cirrhotic and non-cirrhotic patients; all of them achieved SVR rates around 90-100% [16, 8]. Fortunately, OBV/PTV/r regimen is generally considered as lower acquisition cost than that of most sofosbuvir-based regimens [17], and that is an extra-beneficial for the developing countries like Egypt who approved the free charge-based treatment. However, few dedicated real-life studies with these amazing DAA have been done in infected patients with HCV GT4, particularly in Egypt. Thus, the goal of the present investigation was to study the efficacy and safety of OBV/PTV/r plus RBV regimen for 12-weeks treatment of naïve Egyptian patients infected with chronic HCV GT4.

Materials and Methods

Patients' population

Treatment-naive patients with HCV GT4 were undergoing treatment in some centers including governmental hospital at Beni-Suef, Egypt. All eligible patients aged 18-70 years and plasma HCV RNA level >10,000 IU/ml were enrolled in clinical examination and laboratory investigations. Moreover, enrolled patients had liver biochemical markers: albumin<3.5, total bilirubin>1.2 mg/dl, INR>1.2, and platelet count <150,000 mm^3.

The criteria of exclusion in the current study were based on hepatitis of non-HCV causes, coinfection with other than HCV GT4, hepatitis B or HIV infection, poorly controlled diabetics (HbA1C >8) patients, hepatocellular carcinoma, a history of extra-hepatocellular malignancy in the last 5 years, also major severe illness such as congestive heart failure, respiratory failure, evidence of hepatic decompensation. Laboratory and blood picture abnormalities such as anemia (hemoglobin concentration of < 10 g/dl) and thrombocytopenia (platelets <50,000 cells/mm3) and (serum albumin <2.8 g/dL, international normalized ratio (INR) of > 2.3, serum total bilirubin concentration of >3.0 mg/dL.

A cohort involved 108 patients started treatment from 5 January 2017 to 8 September 2017, 100 patients completed the study and 8 patients lost to follow-up. In addition, a written agreement was gained from enrolled patients. The center's ethical committee approved the study protocol that conformed to Egyptian National Guidelines, which were performed according to the Declaration of Helsinki and to Good Clinical Practice guidelines (Decision Date: 08.11.2016).

Study design and treatment

The regimen was compatible with the protocol of the Egyptian National Committee for Control of Viral Hepatitis (NCCVH). The patients enrolled were treated orally with fixed-dose tablets comprising ombitasvir (25 mg), paritaprevir (150 mg), and ritonavir (100 mg), taken with food once daily. Additionally, ribavirin (Copegus ®, Roche, Europe) given oral tablets (total daily dose was dependent on body weight :< 75 kg, 1000 mg; > 75 kg, 1200 mg) and the dose was modified according

to patient tolerability. The study included a number of treatment-naive patients who had advanced liver fibrosis (15/108). The existence of advanced liver fibrosis or compensated liver cirrhosis was documented by the histopathological reading of a liver biopsy or liver stiffness measurements ≥9.5 kPa and/or Fib-4 score >3.25. Efficacy of treatment was expressed by sustained virologic response (SVR12), defined as HCV RNA level under the quantification level (HCV RNA <12 IU/mL) at least 12 weeks after the cessation of treatment.

Assessment of safety and tolerability

All data of adverse events (AEs) were recorded throughout therapy administration up to 30 days post the planned EOT. Safety was assessed by regular clinical examination with physical examination including vital signs, review of any serious adverse events (SAEs). Also, laboratory abnormalities and treatment discontinuations were reported according to WHO criteria.

Laboratory investigations including AST (aspartate transaminase), ALT (alanine transaminase), serum creatinine, serum bilirubin, prothrombin activity, serum albumin and serum α-fetoprotein were done according to the manufacturer's protocol. FIB-4 was estimated on the basis of the equation of Sterling et al. [18]. interleukin28B (IL-28B) genotype was estimated by use of PCR, while HCV GT4 genotyping was assessed by the VERSANT-HCV Genotype 2.0 Assay (LiPA) (Siemens, Germany). Quantitative polymerase chain reaction (qPCR) for HCV was estimated by using AmpliPrep/COBAS TaqMan HCV Test version 2.0 (Roche Diagnostics, Branchburg, NJ), with a lower detection limit < 12 IU/mL Further, hematological parameters were determined using autoanalyzer (MICROS ABX) depending on the manufacturer's protocol.

Informed consent in studies with human subjects

A written agreement was gained from enrolled patients.

Ethical approval

The center's ethical committee approved the study protocol which is conformed to Egyptian National Guidelines which performed according to the Declaration of Helsinki and to Good Clinical Practice guidelines, The approval number is (BSU/2016/11/08). The IBR number of Beni-Suef University is IRB00011029.

Statistical analysis

The statistical difference across continuous variables was analyzed using the t-test. Statistical package SPSS Statistics 21 (IBM, New York, NY) was used for all data analysis. Results are expressed as mean ± standard deviation (SD) or median and number (percentage) for categorical data. In all tests, $P<0.05$ were considered significant.

Results

Overall patient characteristics

100 naive patients completed the treatment therapy, clinical investigations, and analysis, (Figure 1).

Eligible patients were treated 12-weeks with OBV/PTV/r plus RBV. Concerning interleukin -28, patients with non-CC IL-28 β genotype were 77%, while 23% were cc-IL-28β genotype patients. Further, HCV genotype 4a represents 79% of all GT4 patients (Table 1). Seven patients had adverse events (anemia, leukopenia, erythrocytopenia, and thrombocytopenia) leading to ribavirin dose modification. No discontinuation occurred due to adverse events related to doses therapy.

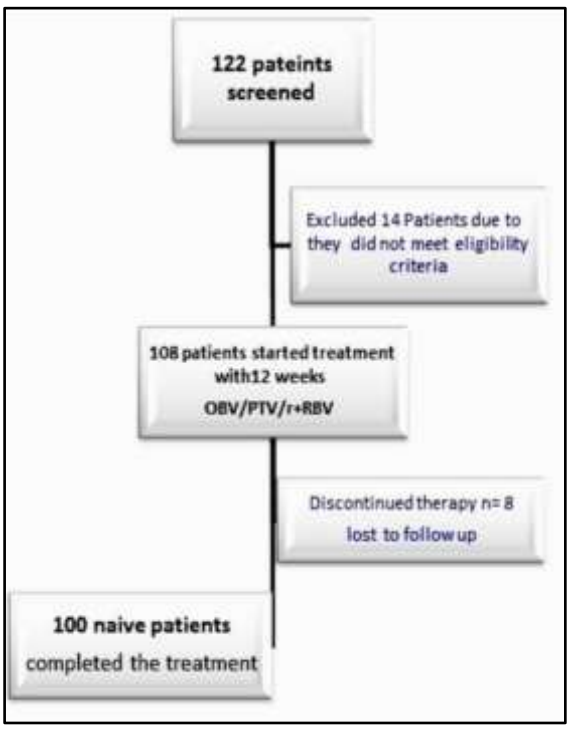

Figure. 1 Patients disposition and the study design. OBV; ombitasvir, PTV; paritaprevir, r; ritonavir. RBV; ribavirin.

Table 1. Demographics and baseline data for treatment naivepatients with OBV/PTV/r plus RBV.

Parameters	Overall
Patients (n)	patients100
Age year (Mean ± SD)	48.9 ± 10.7
Sex (M/F)	45/55
BMI (Mean ± SD)	26.8 ± 4.3
FIB-4 score, n (%)	
<1.45-3.25: None to moderate fibrosis	86(86)
>3.25: Advanced fibrosis or cirrhosis	14(14)
HCV genotype, n (%):	
4a	79(79)
4m	5(5)
4n	7(7)
4o	9(9)
IL28B genotype, n (%):	
CC	23(23)
None-CC	77(77)
Platelets <150 x 10^3/L, n (%)	10(10)
Albumin <3.5 g/dl, n (%)	3(3)
HCV PCR, n (%) <800,000	39(39)
>800,000	61(61)

BMI: Body mass index. HCV, hepatitis C virus, IL28B: Interleukin 28B; PCR: polymerase chain-reaction. Data are presented as mean ± SD or as n (%)

Antiviral response (Efficacy)

The current study revealed high rates of virologic responses and very low rates of relapses after 12-weeks treatment-naive patients with OBV/PTV/r+ RBV, SVR12 rates achieved 97% (97/100) in overall patients**.** Regarding treatment failure, OBV/PTV/r + RBV recorded 3 % (3/100) of patients with treatment failure (0 null-responses and 3 relapses) (Table 2). Moreover, our virologic response was based on "modified intention to treat" analyses (mITT) or per-protocol analysis.

Table 2. Virological response (by modified intention-to-treat (mITT) analysis)

Parameters	Patients (n = 100)
HCV RNA, EOT, n (%)	100(100)
HCV RNA, SVR12, n (%)	97(97)
Virologic failure, n (%)	3(3)
1-Non-Response, n (%)	0(0)
2-Relapsers, n (%)	3(3)
3- Breakthrough, n (%)	0

Note: **Data are presented as n (%).**
HCV, hepatitis C virus; EOT, end of treatment; SVR, sustained virologic response

Safety assessments

Concerning safety and tolerability, OBV/PTV/r+ RBV regimen, adverse events (AEs) occurred in 57 patients (57%) and were generally mild and transient. Most frequently AEs recorded; a headache (28%), asthenia (23%), nausea (19%), fatigue (18%), dyspnea (14%) and decreased hemoglobin concentration (8%). Further, no deaths recorded in the present study, and only 2 patients with serious AEs (SAEs) were reported (patients hospitalization due to bleeding), but not caused discontinuation of the treatment course. While seven patients (7%) had AEs leading to ribavirin dose modification (Figure 1, Table 3). Ameliorations were achieved in terms of the significant decreases in sera AST and ALT activities (P<0.05) after 12 weeks post-treatment relative to those before the commencement of the study (Figure 2). No patients received erythropoietin for managing anemia.

Table 3. Adverse events (AEs) and laboratory abnormalities in overall patients.

Side effects	Patients (n = 100) n (%)
Any adverse event during treatment	57(57)
AEs leading to discontinuation	0
AEs leading to RBV dose modification	7(7)
Serious adverse events	2(2)
Common adverse events	
Headache	28(28)
Asthenia	23(23)
Nausea	19(19)
Fatigue	18(18)
Dyspnea	14(14)
Insomnia	9(9)
Irritability	7(7)
Laboratory adverse events	
Decrease hemoglobin	8(8)
Thrombocytopenia	1(1)
Leukopenia	0
Erythrocytopenia	3(3)
Elevated AST	1(1)
Elevated ALT	0(0)
Hyperbilirubinemia	1(1)

Note: Data are presented as n (%).
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; RBV, ribavirin

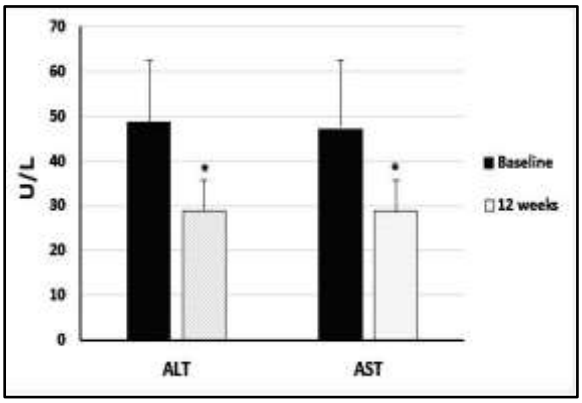

Figure 2. Changes in transaminases at 12 weeks post-treatment among treatment-naive patients treated with OBV/PTV/r plus RBV.

Discussion

Recently, oral DAAs combination regimens are currently achieving viral outcome more than 90% of HCV patients after treatment of 12 weeks [(9)]. Therefore, the strategy of drug combination regimens will become a major idea to prevent treatment failure and relapse. Despite the positive clinical trial outcomes, few studies have provided real-life data regarding HCVGT4 patients, especially in Egypt which has the highest burden of HCV globally. In the present study, the efficacy outcome clear that treatment-naive patients receiving 12 weeks OBV/PTV/r+ RBV achieved 97% (97/100) SVR12 rates, and treatment failure was 3 % (3/100) in overall treated patients. In parallel with our results, Asselah et al. in AGATE-I study revealed that 12 weeks administration of OBV/PTV/r+ RBV achieved 97% SVR12 rate of patients with compensated cirrhosis, and 98% after 16 weeks treatment. Moreover, the authors added that OBV/PTV/r with RBV achieved 100 % SVR12 when administered for 12 weeks to non-cirrhotic naive and experienced patients [(19)]. In other trial, AGATE-II, multicenter, phase III trial performed in treatment-naïve or-experienced Egyptian patients infected with chronic HCV GT 4, Waked et al. indicated that 12 weeks treatment of OBV/PTV/r + RBV achieved 94 % SVR12 rate in non-cirrhotic patients, while in cirrhotic cases SVR12 was 97% or 93 % after treatment for 12 or 24 weeks, respectively [(20)]. In El Kassas *et al*. study, experienced patients who received 24 weeks of OBV/PTV/r/RBV resulted in 100 % SVR 12. While the addition of SOF to the OBV/PTV/r/RBV regimen resulted in 97 % SVR after 12 weeks of treatment [(21)].

Moreover, Flisiak et al. [(22)], in real-world evidence, have been deduced the antiviral potency of OBV/PTV/r- dasabuvir (DSV)-RBV in the road of treatment of HCV GT (1&4) infections. Additionally, Wedemeyer et al. revealed that OBV/PTV/r+ DSV± RBV therapy achieved high rates of SVR12 in the treatment of HCV-GT (1&4). Whereby, overall viral outcome achieved SVR12 rates of 96.8% for GT1 and 98.9% for GT4 infection [(23)]. Interestingly, the addition of RBV to DAAs regimens had a significant issue for treating patients with HCV GT4 because GT4 has multiple heterogeneous subtypes [(24)]. On the other side, the multi-targeted regimen of SOF plus OBV/PTV/r + RBV was well tolerated and achieved excellent SVR rates (97%; 109/113) among retreatment-experienced Egyptian patients with prior DAA treatments failure [(25)]. Moreover, our results cleared that baseline characteristic including gender, age, BMI, HCV-RNA levels, GT4 subtype and IL-28β genotype, may not impact on the virologic outcome. In the era of oral DAAs combination therapies, the positive feedback of the CC IL-28β genotype varies by type of treatment regimen [(26)]. IL-28, which activates interferon-stimulated genes, is the orchestra maestro of innate immunity against HCV burden [(27)]. So, the present study, which achieved SVR12 rate of 97% in overall patients, covers the most patients that had non-CC IL-28β genotype (77%), suggesting that this host genotype does not have negative feedback on the virological outcome when treated with the current therapy. On the other hand, an alternative interpretation is that the

excellent SVR12 was achieved regardless of IL28β genotype.

It was also revealed that the improved liver disease markers were maintained 3 years post treatment of patients with GT1 [28]. On the other hand, duration extension of treatment to 24 weeks did not show boosted efficacy than that of 12 or 16 weeks. [29].

The profile of DAAs combination regimens was favorable and safety, and the tolerability of regimen was mostly mild or moderate in our real-life cohort. Common AEs reported in our study observed in 57% of patients were headache (28%), fatigue (18%), asthenia (23%), nausea (19%), dyspnea (14%) and decreased hemoglobin concentration (8%). The current data were in line with that reported in AGATE-I trial; the most of AEs were of mild to moderate in severity. Whereby the most frequently reported AEs were asthenia (18%), fatigue (17%), headache (23%) and anemia (15%) [19]. Also, in PEARL-I study where treatment-naive patients were treated with OBV/PTV/r ± RBV, AEs were 77 and 88 %, respectively [30]. Additionally, the most common AEs reported by OBV/PTV/r plus RBV regimen were headache (41%) and fatigue (35%) in chronic HCV GT4 Egyptian patients without cirrhosis in Waked et al., study [20].

The limitations of our study are the small sample of patients and the absence of treatment-experienced patients. Further, the study includes the absence of baseline resistance tests.

Conclusion

The interferon-free regimen of DAAs combination, OBV/PTV/r plus RBV, achieved high SVR12 rates with virologic outcome failures 3% (0% null-responses, 3% relapses). This regimen also achieved high SVR regardless of IL28B genotype. Moreover, the regimen was generally safe and well tolerated with no drug interruptions or discontinuations due to different adverse events in treatment-naive patients with chronic HCV-GT4 infection in Egypt. Further studies are required to sketch a complete picture describing the relationship between IL-28β genotypes and each of IFN-free regimens outcomes.

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Conflict of Interest

We declare that there is no conflict of interest and we did not get any type of funds for this experiment nor for publishing.

Credit Author Statement

Mohammed Abdel-Gabbar

Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

Mohammed Alkot

Conceptualization; Investigation; Methodology; Visualization; Roles/Writing - original draft; Writing - review & editing.

Adel Abdel-Moneim

Conceptualization; Data curation; Methodology; Project administration; Resources; Software; Validation; Supervision; Visualization; Roles/Writing - original draft; Writing - review & editing.

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