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EFFECTIVENESS OF OMBITASVIR/PARITAPREVIR/RITONAVIR +/- DASABUVIR FOR TREATMENT OF CHRONIC HCV INFECTION BY GENOTYPES 1 OR 4 IN MONO- AND HIV CO-INFECTED PATIENTS

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ABSTRACT **OBJECTIVES:** To analyze the effectiveness of ombitasvir-paritaprevir-ritonavir (OBV/PTV/rtv) with or without dasavubir(DSV) in a real-life cohort of patients with chronic HCV infection; to establish the influence of HIV coinfection on success rates; and to examine resistance mutations in patients with virological failure.

METHODS: Observational,retrospective,multi-centre study conducted in HCV patients who received OBV/PTV/rtv.The proportion of patients with undetectable HCV-RNA at 12 weeks after the end of treatment(SVR12) was calculated using modified intention-to-treat(mITT) and per-protocol(PP) analyses.

RESULTS: The study included 136 patients with median age of 51 years,63.2 % were coinfected with HIV;39.7 % had received previous antiviral treatment for HCV infection; 14.1% had cirrhosis;30.1 % were genotype 1a,39.7% genotype 1b and 25% genotype 4; 93.4% received OBV/PTV/rtv ± DSV for 12 weeks, 47.8% received this treatment plus ribavirin; 2.2% of patients discontinued the treatment. Effectiveness was 93.2 % by ITTm analysis and 96.1 % by PP analysis. These outcomes were not affected by coinfection with HIV (p=0.2). Virological failure was recorded in 4 patients (3.1%).Resistance mutations against NS5A were detected in three patients (75% of failures).

CONCLUSIONS: These data confirm the high success rates reported by clinical trials for OBV/PTV/rtv plus DSV.Virological failure with OBV/PTV/rtv±DSV appears to mainly affect NS5A polymerase.

KEYWORDS : OMBITASVIR/PARITAPREVIR, DASAVUBIR, HIV, HCV.

INTRODUCTION

According to the latest report of the World Health Organization in 2017, chronic hepatitis C virus (HCV) infection affects 325 million people worldwide (1). Before the availability of oral direct-acting antivirals (DAAs), patients with chronic HCV genotype 1 or 4 (G1 or G4) infection were treated using pegylated interferon and ribavirin (PR) with a relatively low likelihood of success, obtaining a sustained virological response (SVR) in only 45-55 % of these patients (2). Furthermore, multiple adverse effects favoured abandonment of the treatment, which could not even be initiated in some patients with severe thrombopenia, autoimmune or neuropsychiatric diseases, among others (3). The emergence of first-generation DAAs, Telaprevir (TPV) and Boceprevir (BOC), whose activity is limited to GT1, led to an improvement in SVR rates from 45 to 75 %, mainly in patients previously treated with PR (4, 5); however, the appropriate posology for first-generation NS3/4A protease inhibitors remained problematic, and numerous adverse effects were reported, including pruritus, exanthema and anaemia (4, 5). The subsequent development of more effective DAAs that act simultaneously on different HCV targets, some co-formulated in a single pill, (6), facilitated treatment adherence and minimized adverse effects (7).

One drug combination available to treat chronic infection by HCV GT1 is ombitasvir/paritaprevir/ritonavir and dasabuvir (OBV/PTV/rtv and DSV), designated 3D, associated or not with ribavirin (RBV). It comprises an NS5a enzyme inhibitor (ombitasvir), (NS)3/4A non-structural protease inhibitor (paritaprevir), CYP3A cytochrome inhibitor (ritonavir) and NS5B polymerase non-nucleoside inhibitor (dasabuvir) (8). In patients with genotype GT1a, clinical trial data support the combined administration of 3D with RBV for 12 weeks,

which achieved SVR rates in 95-97 % of non-cirrhotic patients and 91.8 % of patients with Child's stage A cirrhosis; a higher rate was observed in cirrhotic patients with null response to PR who received this treatment for 24 (94.2 %) *versus* 12 (88.6 %) weeks (9). In patients with GT1b, the SVR rate was 96-100 % after administering 3D for 12 weeks, with or without RBV (10).

OBV/PTV/rtv without DSV is designated 2D and is indicated to treat genotype 4.A clinical trial in GT4 mono-infected patients reported a SVR of 100 % in naïve and pretreated patients without cirrhosis and 97 or 98 % in compensated cirrhotic patients receiving 2D plus RBV for 12 or 16 weeks, respectively (10).

The design of CTs excludes many types of patient seen by clinicians, In addition, the findings of other European or Spanish cohort studies (11, 12) cannot be completely extrapolated to our population, and none has compared mono-infected with HIV-coinfected HCV patients. With this background, the objectives of this study were to: perform a real-life analysis of the effectiveness of 3D/2D in patients with chronic HCV GT 1 or 4 infection in our setting, to study the effectiveness of 3D/2D as a function of HIV coinfection, and to analyze cases of virological failure and its repercussions on future DAA treatments.

PATIENTS AND METHODS

- **Design:** a multicentre retrospective study was conducted in patients with chronic HCV G1 or G4 infection treated with OBV/PTV/rtv with or without DSV and attending Infectious Disease Departments/Units of public hospitals in the Andalusian Autonomous Community (Southern Spain).

- **Inclusion criteria:** age ≥18 years, infection with HCV GT1 or G4, and treatment with OMB/PTV/rtv±DSV.

- **Study variables:** age, sex, HCV viral load at baseline and at ≥ 12 weeks after treatment with 3D or 2D (SVR12), genotype (GT), transient elastography score, platelet count, Child-Pugh score, MELD score and history of HCV treatment. In HIV-positive patients, data were also gathered on antiretroviral treatment, HIV viral load and lymphocyte subpopulations.

- **Transient elastography :** a FibroScan device (Echosens ™, Paris, France, Model 502) was used to determine the fibrosis degree (fibroscan [FS] score) at an outpatient visit under fasting conditions with patients in supine position. The probe was placed on the last right intercostal space in the medium axillary line and perpendicular to the skin plane. At least 10 valid measurements were conducted, and the value obtained was considered adequate when a success rate > 60 % was achieved (13). We considered FS <7.6 kPa = F0 - F1; 7.7 – 9.4 kPa = F2; 9.5 - 14 kPa = F3; >14 kPa = F4.

NS5B polymerase, NS3 protease and NS5A protein were sequenced in patients who did not achieve SVR12, using assays based on the Sanger method developed at our centre (14). Resistance-associated substitutions (RASs) in these three targets were scored according to Lontok et al. (15).

DEFINITION OF VARIABLES:

SVR from week 12 (SVR12) was defined by the absence of any HCV particle or virus in blood at ≥12 weeks after completion of 3D/2D treatment.

Treatment success was defined by a SVR for ≥ 12 weeks (SVR12) after completion of the anti-HCV treatment regimen.

Null responder was defined by the failure to reduce RNA-HCV by > 2 log IU/mL at week 12 of HCV antiviral treatment (16).

Partial responder was defined by the reduction of RNA-HCV > 2 log IU/mL at week 12 of HCV antiviral treatment but the detection of RNA-HCV at week 24 (16).

Relapse was defined by the absence of detectable RNA-HCV during treatment but its detection after the end of treatment (16).

STATISTICAL ANALYSIS

Descriptive analysis: Central tendency and dispersion measurements (mean, standard deviation, median, percentiles) were determined for quantitative variables and absolute frequencies with 95 % confidence interval for qualitative variables. The percentage of patients achieving SVR12 was calculated.

Effectiveness analyses: Effectiveness was determined in two ways: a modified intention-to-treat (mITT) analysis, including all patients except those lost to the follow-up or with no available SVR12 data; and a per-protocol (PP) analysis, only including those who completed treatment with available HCV RNA results at ≥12 weeks post-treatment.

SPSS 20.0 software was used for statistical analyses.

RESULTS

Baseline patient characteristics

The study included 136 patients with a mean age of 51 years; 74.3 % were male, 62.3 % were coinfected with HIV and 39.7 % had a history of HCV treatment. Further data on their characteristics are exhibited in Table 1.

Genotype distribution was: GT1a in 30.1 %, GT1b in 39.7 % and G4 in 25%. Fibrosis degree (FS stage) distribution was: F1 in 30.9 %, F2-F3 in 52.9 % and F4 in 14.7 %. Table 2 also displays results for the remaining HCV-related study variables.

HCV treatment with 3D or 2D was received for 12 weeks by 93.4 % of patients, 24 weeks by 5.1 % and 16 weeks by 1.5 %. 3D or 2D was combined with weight-adjusted RBV (weight ≤ 75 kg, 1000 mg; >75 Kg, 1500 mg) in 47.8 % of patients. RBV was administered to 72.7 % of patients with genotype GT4, 67.5 % of those with GT1a and 15.1 % of those with GT1b. Further data are reported in Table 3.

mITT and PP analyses

Out of the 136 patients enrolled in the study, the treatment was discontinued by three (2.2 %), by patient request in one case and due to adverse effects in the other two (rash, insomnia). Three patients (2.2 %) died before the SVR12 verification date; these deaths were not attributable to the treatment (suicide in one case). Out of the remaining 130 patients (95.5 %), 3 (2.3 %) were lost to the follow-up and the treatment failed in 4 (3.1 %), while 123 (94.6 %) met the criterion for successful treatment (SVR12).

The global effectiveness of the combination was 92.5 % in the mITT analysis (123/133).

The PP analysis yielded a global SVR12 rate of 94.6 %; for GT1a genotype, it was 97.5 % (100 % with RBV and 92.3 % without); for GT1b, 92.5 % (100 % with RBV and 91.1 % without); and for GT4, 84.8 % (83.3 % with RBV and 88.9 % without. Other findings are displayed in Table 3.

Coinfected *vs*. non-coinfected patients treated with 3D/2D

No difference was found between patients with HIV coinfection and those without in: sex (p=0.39), age (p=0.16), previous HCV treatment (p=0.25), cirrhosis (p=0.8), 3D/2D treatment duration (p=0.729), baseline HCV viral load (p=0.68) or SVR (p= 0.2). However, they differed in genotype, with a greater proportion of GT1a and GT4 infections in coinfected patients (38.4 *vs*. 16 %, p=0.006 and 29.1 *vs*. 18 %, p=0.151, respectively) and of GT1b in non-coinfected patients (62 *vs*. 26.7 %; p=0.001) (Table 4).

No statistically significant differences were found in the effectiveness (SVR12 rate) of 3D/2D treatment as a function of HCV viral load (p= 0.5), treatment time (p= 0.6), GT (p= 0.2), combination with RBV (p= 0.4), or the presence of cirrhosis (p= 0.5) or HIV coinfection (p= 0.2) (Figure 1).

VIROLOGICAL FAILURE

Out of the 130 patients studied, SVR12 was not achieved by four (3.1 %), who were all coinfected with HIV and represented 4.7 % of seropositive patients: one patient with GT1a, F4 fibrosis, cirrhosis, who had been pretreated with PR and received 3D for 12 weeks without RBV; two patients with G1b, F2/F3 fibrosis, one naïve and the other pre-treated with PR, who received 3D for 12 weeks without RBV; and one patient with GT4, F1 fibrosis, with previous failure to sofosbuvir/ledipasvir who received 2D treatment with RBV for 12 weeks. As detailed in table 5, resistance study of the four cases of

virological failure detected resistance mutations to NS5a inhibitors (Q30R, Q30L, Y93H).

DISCUSSION

This study included patients with chronic HCV infection (genotype 1 or 4) treated with 3D or 2D in public hospitals of the Andalusian Health System. They were typically middle-aged and male, while coinfection with HIV was observed in more than half of the patients, who were all receiving antiretroviral therapy and had good virological and immunological control. Thirty-four percent of patients had a history of HCV treatment, to which almost 50% were null responders, 31.3% had relapsed and 12.5% discontinued treatment due to adverse effects. The most frequent genotype was G1b (62% of patients), followed by GT1a and GT4. The most frequent FS fibrosis stage was F2-3, recording F4 in only 14.7 % of the patients. The median Child-Pugh score was 5 and median MELD score was 7.

OMV/PTV/rtv±DSV treatment obtained the highest success (SVR12) rate in patients with genotype GT1a infection (97.5 %), followed by those with GT1b (92.5 %) and G4 (< 90 %). In GT1a cases, the best outcomes were obtained for treatment with 3D plus RBV, which achieved a 100 % success rate, while high rates were also recorded for 3D without RBV (92.3 %). Similar results were obtained in GT1b cases, with a success rate of 100% for 3D plus RBV and 91.1 % for 3D alone. These data may suggest that it is not always necessary to combine 3D with RBV in GT1a cases, as recommended in the guidelines (17, 18), and that RBV could be omitted in selected patients. In GT1b cases, the addition of RBV is not recommended in guidelines (18, 19) but would appear to benefit a sub-group of these patients. Further studies are required to identify patients who do and do not benefit from the combination of 3D with RBV.

The success rate in our real-life cohort was within the range (SVR12 in 87-100 %) reported by previous clinical trials and observational studies in patients with GT1a infection treated with 3D, with or without RBV (12, 20-22). However, the success rate observed in patients with GT4 infection was lower than previously reported (21, 23-25), even in cirrhotic patients, with or without RBV. Thus, five (15.5 %) of the thirty-three patients with GT4 infection did not achieve SVR12, although only one experienced virological failure, resulting in a virological failure rate of 3 %, similar to previous findings (21, 23-25) With regard to the cause of treatment failure, NS5A resistance mutations were found in two of the thirteen patients, one of whom (with GT1a infection and cirrhosis) did not receive the recommended treatment with RBV, whereas no cause of failure was identified in the other; in the other ten cases of failure, this was attributable to cessation of the treatment by six patients, due to adverse reaction in two and patient request in the other one, while three died before reaching 12 weeks post-treatment, with no death being caused by the treatment.

In our cohort of patients treated with 3D/2D, coinfection with HIV was not a predictive factor for a poor response, with a success rate > 90 %, slightly higher than the rates of 88.9 % observed in patients receiving 3D without RBV and 88.7 % in those receiving 3D with RBV in a recent study of HIV-coinfected veterans with GT1 infection (22). No differences were found between the presence and absence of cirrhosis (90 *vs.* 92.8 %) or between genotypes GT1a (97.5 %) and G1b (92.5 %). A previous real-life study reported similar data, achieving SVR12 rates of 94.7 % in cirrhotic patients *versus* 96.4 % in non-cirrhotic patients and rates of 93.1 % in GT1a cases and 99.2 % in GT1b cases (26). However, the aforementioned study of coinfected veterans with GT1 described a lower success rate in patients with cirrhosis than in those without (85.9 vs. 92.4 %, p = 0.006)] (22). A CT in 22 HIV-coinfected patients (GT1 a or b) had a similar proportion of cirrhotic patients to that in the present cohort and obtained a SVR12 rate of 100 % (20).

Resistance tests in the patients with true virological failure were similar to previous results, detecting resistance-associated mutations in NS5A in almost all patients. Given that NS5A RASs persist over time and therapeutic rescue options are based on regimens that include anti-NS5A agents (27), this may limit future treatment options for these patients. However, the recent approval of combinations with new drugs (VoseviTM- Sofosbuvir, Velpatasvir, Voxilaprevir [28, 29]; MavyretTM- Glecaprevir, Pibrentasvir [30]) may reduce the impact of these RASs.

In conclusion, our data confirm the high SVR rates previously reported for OMV/PTV/rtv with or without DSV in patients with chronic HCV GT 1 or 4 infection with or without HIV coinfection. Resistance mutations in NS5A polymerase were observed in almost all patients who experienced virological failure, for whom an alternative therapeutic regimen is required.

Table 1. Baseline characteristics of treated patients

	N = 136
Age, yrs, median (P25-P75)	51 (46-55)
Male gender, n (%)	101 (74.3)
HIV, n (%)	86 (63.2%)
Receipt of ART by HIV patients, n (%)	86 (100)
• NRTI	68 (79.1)
• NNRTI	21 (24.4)
• PI	30 (34.9)
• II	47 (54.7)
Baseline RNA-HIV, copies/mL, median (P25-P75)	0 (0-0)
Baseline RNA-HIV < 50 copies/mL, n (%)	133 (97.8)
Baseline CD4, cell/uL, median (P25-P75)	620 (366-835)
Previous HCV treatment, n (%)	54 (39.7)
• Null responder, n (%)	26 (48.1)
• Relapse, n (%)	15 (27.8)
• Cessation for adverse effect, n (%)	8 (14.8)
• Partial responder, n (%)	3 (5.5)

ART: antiretroviral treatment; **NRTI:** nucleoside-analogue reverse transcriptase inhibitor; **NNRTI:** non-nucleoside-analogue reverse transcriptase inhibitor; **PI**: protease inhibitor; **II:** integrase inhibitor.

Table 2. Baseline HCV infection-related characteristics

	N = 136
Previous baseline HCV viral load,(log), median (P25-P75)	6.24 (5.78-6.6)
Genotype, n (%)	
• 1a	41 (30.1)
• 1b	54 (39.7)
• 1(ND)	7 (5.1)
• 4	34 (25)
Fibrosis (fibroscan), n (%)	
• F1	42 (30.9)
• F2	31 (22.8)
• F3	41 (30.1)
• F4	20 (14.7)
• Not conducted	2 (1.5)
MELD, median (P25-P75)	7 (6-9)
Child-Pugh, median (P25-P75)	5 (5-5)
Cirrhosis, n (%)	20 (14.7)
2D or 3D treatment duration, n (%)	
• 12 weeks	127 (93.4)
• 16 weeks	7 (5.1)
• 24 weeks	2 (1.5)
• 2D or 3D with RBV, n (%)	65 (47.8)

1(ND): Genotype 1 without subtyping; **RBV**: ribavirin, **2D** (ombitasvir/paritaprevir/ritonavir), **3D** (ombitasvir/paritaprevir/ritonavir + dasabuvir)

Table 3. Chronic HCV infection treatment and outcomes

Genotype, n* (%)	Ribavirin n (%)	SVR12 n (%)	SVR GT** n (%)
1a 40 (29.4)	Yes 27(67.5)	Yes 27(100)	39 (97.5)
		No 0	
	No 13(32.5)	Yes 12(92.3)	
		No 1(7.6)	
1b 53(38.9)	Yes 8(15.1)	Yes 8(100)	49 (92.5)

		No	0	
	No 45(84.9)	Yes 41(91.1)		
		No	4(8.9)	
1(ND) 7(5.1)	Yes 5(71.4)	Yes 5(100)		7 (100)
		No	0	
	No 2(28.5)	Yes 2(100)		
		No	0	
4 33(24.3)	Yes 24(72.7)	Yes 20(83.3)		28 (84.8)
		No	4(16.7)	
	No 9(27.3)	Yes 8(88.9)		
		No	1(11.1)	

SVR12: sustained virological response for ≥ 12 weeks. **GT**:** genotype. **1(ND)**: Genotype 1 without subtyping;

Table 4. Comparison between HIV-coinfected and non-coinfected patients

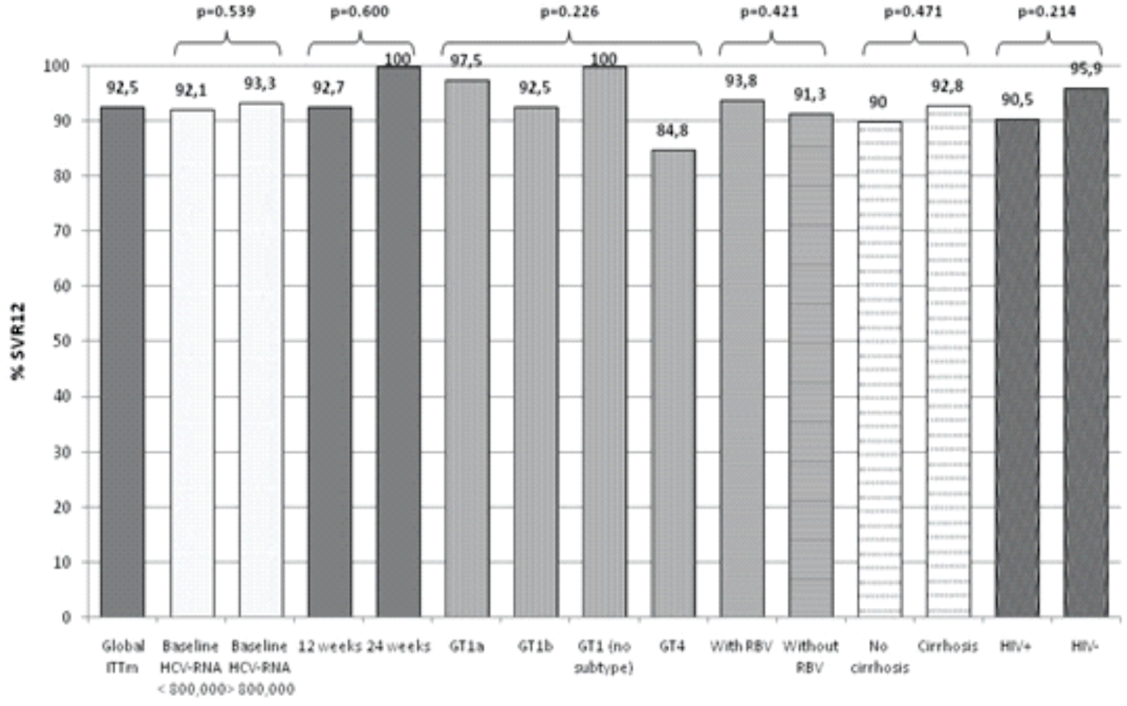
Variable	Non-coinfected n= 50	Coinfected n= 86	P value*
Age (yrs), mean±SD	52.5±11.6	50±60	0.161
Male gender, n (%)	35 (70)	20 (76.7)	0.386
Genotype, n (%)			<0.001
- 1a	8 (16)	33 (38.4)	0.006
- 1b	31 (62)	23 (26.7)	0.000
- 1 (without subtyping)	2 (4)	5 (5.8)	0.490
- 4	9 (18)	25 (29.1)	0.151
Previous anti-HCV treatment, n (%)	17 (34)	37 (43)	0.253
Previous response, n (%)			1
- Partial responder	1 (6.3)	2 (5.6)	
- Null responder	8 (50)	18 (50)	
- Treatment interruption	2 (12.5)	6 (16.7)	
- Relapse	5 (31.3)	10 (27.8)	
Cirrhotic, n (%)	7 (14)	13 (15.1)	0.817
Ribavirin, n (%)	16 (32)	49 (57)	0.005
Treatment duration, weeks, n (%)			0.729
- 12	48 (96)	79 (91.9)	
- 16	0	2 (2.3)	
- 24	2 (4)	5 (5.8)	
Baseline HCV-VL > 800.000 UI/mL, n (%)	35 (70)	57 (66.3)	0.680
Sustained virological response, n (%)	47 (95.9)	76 (90.5)	0.214

HCV-VL: HCV viral load; **p***: significance <0.05

Table 5. Description of patients with failure to ombitasvir/ paritaprevir/ritonavir±dasabuvir

Subject	Age	Sex	HIV+	ART	Pretreated	RP	GT	FS	Baseline HCV VL	Albumin <3.5 g/dL	RBV	Duration weeks	RS
1	51	Male	YES	DRV/r	Peg-IFN + RBV	NR	1b	F2-F3	Unknown	Unknown	No	12	Q30R (NS5A)
2	50	Male	YES	DRV/r + DTG	Peg-IFN + RBV	Ceased for A.E.	1a	F4	2,720,000	No	No	12	Q30L (NS5A)
3	48	Male	YES	ABC/3TC + DRV/r	SOF + LDV	NR	4	F1	788,000	No	Yes	12	Without mutations
4	51	Male	YES	TDF/FTC + ATV	Naïve	-	1b	F2-F3	2,190,000	No	No	12	Y93H (NS5A)

ART: antiretroviral treatment; RP: response to previous HCV treatment (null, partial, relapse); NR: null responder; GT: HCV genotype; FS: fibroscan stage; HCV VL: HCV viral load; peg-INF: pegylated-interferon; RBV: ribavirin; SOF+LDV: sofosbuvir+ ledipasvir; RS: resistance study; AE: adverse event; DRV/r: darunavir/ritonavir; DTG: dolutegravir; ABC/3TC: abacavir/lamivudine, ATV: atazanavir; TDF/FTC: tenofovir/emtricitabine.



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