

Review article

Real-world experience with ombitasvir/paritaprevir boosted with ritonavir and possibly combined with dasabuvir and ribavirin in HCV infection

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Abstract

Ombitasvir/paritaprevir boosted with ritonavir and possibly combined with dasabuvir and ribavirin (OBV/PTV/r ± DSV ± RBV) is a new direct-acting antiviral (DAA) regimen which has improved efficacy of chronic hepatitis C virus (HCV) treatment significantly. OBV/PTV/r ± DSV ± RBV in clinical trials demonstrated sustained viral response (SVR) rates close to 100%. In this article we collected currently available data of 5726 patients for evaluation of OBV/PTV/r ± DSV ± RBV efficacy and safety in real-world experience. The sustained viral response rate in this large population was 97%, and it was exactly the same even in patients with liver cirrhotics. According to this meta-analysis, less than 3% of patients discontinued treatment due to adverse events.

Key words: HCV, paritaprevir, ombitasvir, dasabuvir.

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Introduction

Direct-acting antiviral (DAA) regimens improved the efficacy of chronic hepatitis C virus (HCV) treatment. Ombitasvir, paritaprevir boosted with ritonavir and possibly combined with dasabuvir and ribavirin (OBV/PTV/r ± DSV ± RBV) were licensed in the European Union in 2014 for use as a combination therapy for HCV infection [1, 2]. OBV/PTV/r ± DSV ± RBV became reimbursed in Poland for patients infected with genotype 1 and 4, irrespectively of fibrosis or previous treatment history starting from July 2015 as the first available interferon-free regimen and included in clinical practice guidelines issued by the Polish Group of HCV Experts [3]. However, early access to these innovative medications has been provided since November 2014, mostly for patients with advanced liver fibrosis, who were included in the AMBER real world study [4-6]. Similar real-world studies were carried out in numerous countries and preliminary results became available during the European Association for the Study of the Liver (EASL) International Liver Congress

in Barcelona in April 2016 (ILC-EASL 2016). In this article we have collected currently available data on the efficacy and safety of OBV/PTV/r ± DSV ± RBV in real-world practice, which have been presented recently.

Characteristics of the regimen

The three DAA – ombitasvir (OBV), paritaprevir (PTV) and dasabuvir (DSV) – are formulated into two tablets and manufactured by AbbVie. Viekirax, which contains 12.5 mg of OBV plus 75 mg of PTV boosted with 50 mg of ritonavir (OBV/PTV/r) and Exviera, consists of 250 mg of DSV as sodium monohydrate. According to the products' characteristics, OBV/PTV/r ± DSV ± RBV are dedicated for the treatment of chronic hepatitis C in adults infected with genotype (GT) 1 and 4 [7, 8]. Therapy for genotype 1a and 1b is based on a fixed-dose regimen that includes OBV/PTV/r taken as 2 tablets once daily, and DSV in the second tablet taken twice a day. OBV/PTV/r without DSV is used for treatment of patients infected with GT4. The addition of a weight-adjusted dose of RBV is required in all patients

infected with genotype 1a and 4 HCV. According to the most recent label, RBV is not required in patients infected with genotype 1b, which is predominant in Central Europe. The standard duration of therapy is 12 weeks for GT1b infection without cirrhosis and with compensated cirrhosis. Patients infected with GT1a without cirrhosis should be treated in combination with RBV for 12 weeks, and in the case of those with compensated cirrhosis treatment should be extended to 24 weeks.

OBV/PTV/r ± DSV therapy should not be used in patients with advanced liver failure and a Child-Pugh score of C. Patients with a history of hepatic decompensation including patients with a Child-Pugh score of B can be considered for treatment under close monitoring in experienced hepatologic centers [3].

Real-world experience

Phase 3 clinical trials carried out with OBV/PTV/r ± DSV ± RBV have shown SVR rates exceeding 90%,

irrespective of genotype, liver fibrosis or previous history of treatment [9]. Real-world data usually provide efficacy lower compared to clinical trials because they include more divergent and non-adherent populations. In a number of real world studies presented in Table 1, OBV/PTV/r ± DSV ± RBV based treatment was effective as it was demonstrated in clinical trials and achieved high rates of SVR12 in the range of 91-100%, irrespective of liver fibrosis, previous history of treatment or genotype. As shown in Table 2 this regimen was well tolerated in adults and was associated with low rates of treatment discontinuation.

The first interim analysis carried out in the AMBER study was presented during the Viral Hepatitis Congress in Frankfurt in 2015 and demonstrated a fast virologic response, similar to that observed in registration studies [4]. Final data also confirmed the SVR12 rate of 99% in a population of 209 patients consisting mostly of GT1b infected, cirrhotics and non-responders to previous therapy, including failures of triple

Table 1. Overview of efficacy in real-world studies with OBV/PTV/r ± DSV ± RBV in HCV infection

Reference	Country	Number of patients <i>n</i>	Proportion of known genotypes 1/1a/1b/4 <i>n</i>	Cirrhosis <i>n</i> (%)	SVR 12 in all patients <i>n</i> (%)	SVR 12 in cirrhosis <i>n</i> (%)
Aghemo [14]	Italy	42		42 (100)	41 (98)	41 (98)
Calleja [11]	Spain	1422	8/247/1312/0	732 (47)	1376 (97)	710 (97)
Christensen [15]	Germany	87			83 (95)	
Derbala [16]	Qatar	42	0/0/0/42	24 (36)	41 (98)	24 (100)
Flisiak [6]	Poland	209	11/13/176/9	119 (57)	207 (99)	117 (98)
Gomez [17]	Spain	31			31 (100)	
Hinrichsen [18]	Germany	558	0/141/351/53	127 (24)	539 (97)	129 (95)
Hunyady [13]	Hungary	61	61/0/0/0		60 (98)	
Jeruma [19]	Latvia	15	0/0/15/0	15 (100)	15 (100)	15 (100)
Londono [20]	Spain	37			36 (97)	
Lubel [21]	Australia	167	167/0/0/0		167 (92)	(91)
Mateya [22]	Bulgaria	62			61 (98)	
McCombs [12]	USA	1012	773/0/0/0	350 (35)	945 (93)	329 (94)
Ouzan [23]	France	20	15/0/0/5		20 (100)	
Perello [24]	Spain	77			75 (97)	
Petta [25]	Italy	728		728 (100)	712 (98)	712 (98)
Rincon [26]	Spain	547			538 (98)	
Teti [27]	Italy	193	193/0/0/0		188 (97)	
Zuckerman [10]	Israel	416	416/0/0/0	253 (62)	413 (99)	251 (99)
Overall		5726	1644/401/1854/109	2390 (54)	5548 (97)	2328 (97)

Table 2. Available safety data of OBV/PTV/r ± DSV ± RBV treatment in real-world experience

Reference	Patients discontinued due to adverse events <i>n</i> (%)	Patients with hepatic decompensation <i>n</i> (%)	Serious adverse events <i>n</i> (%)
Calleja [11]	24 (1.8)	8 (0.5)	84 (5.4)
Flisiak [5, 6]	5 (2.4)	7 (3.3)	8 (3.8)
Hinrichsen [18]	8 (3)	0	13 (2)
Hunyady [13]	0	0	3 (3.8)
Lubel [21]	3 (1.1)	6 (2.2)	9 (3.4)
Zuckerman [10]	20 (3)	8 (1.2)	25 (3.8)

regimens [6]. Serious adverse events (SAEs) were observed in 8 patients (3.8%), and 5 patients (2.4%) discontinued treatment due to adverse events (AE). Risk of on-treatment decompensation was associated with a history of decompensation before the treatment and baseline hepatic function [5]. Adverse events were observed in 151 patients (72%), and they were mostly related to RBV [6]. Almost exactly the same efficacy (SVR rate 99%) and safety results were achieved by Zuckerman *et al.* [10] in a population of mostly cirrhotic Israeli patients infected with genotype 1 (subgenotyping not available).

The highest number of enrolled patients was in the multicenter Spanish study presented at the ILC-EASL 2016 by Calleja *et al.* [11]. The analysis covered 1422 GT1 (mostly GT1b) infected patients; 49% of them were treatment experienced, and 47% were cirrhotics. The SVR12 rate in this population was 97%. In a multivariate analysis, a decreased probability of achieving SVR was associated with low baseline albumin. No statistical differences were associated with genotype, age or stage of fibrosis. Serious adverse events occurred in 84 patients (5.4%) and 1.8% discontinued early. The most frequent SAE was anemia, associated with RBV (24 patients, 1.5%), skin lesions (11 patients, 0.7%) and infections (8 patients, 0.5%). Occurrence of SAEs was related to MELD score, high transient elastography values and advanced age.

Another large real world study was presented by McCombs *et al.* [12] from the United States Veterans Health Administration. They carried out an analysis of 1012 patients infected mostly with GT1 (76%), 1/3 with liver cirrhosis, and the final efficacy rate was 93%. In this study HBV and HIV coinfections, as well as diabetes and obesity, were found to have no statistically significant impact on the likelihood of achieving SVR 12.

In a relatively small but important study Hunyady *et al.* [13] demonstrated that failure of the interferon-based triple regimen containing the first generation protease inhibitor boceprevir or telaprevir did not

affect the high efficacy of OBV/PTV/r ± DSV ± RBV (SVR rate 98%).

Treatment of 5726 patients, including 2390 cirrhotics, with OBV/PTV/r ± DSV ± RBV in real-world studies with currently available data was safe and therapeutic success was achieved by 5548 patients, so the SVR rate calculated in this metaanalysis was 97% in both the general population and in patients with liver cirrhosis (Table 1). The discontinuation rate due to AE did not exceed 3%, and SAEs were observed in 2-5.4% of patients (Table 2). Anemia and hyperbilirubinemia occurred usually in cirrhotics receiving RBV [21]. However, due to the exclusion of RBV from the regimen for GT1b patients, according to the most recent label, this problem should disappear in a large majority of European patients.

According to results of randomized clinical trials, the OBV/PTV/r ± DSV ± RBV regimen has been found to fulfill the promise of SVR rates close to 100%. However, the most important requirement is confirmation of such high efficacy in real-world experience in the large, mixed population of patients previously considered as “difficult to treat”.

Disclosure

The authors report no conflict of interest.

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