Research Article

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Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort

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Background & Aims: Clinical trials evaluating second-generation direct-acting antiviral agents (DAAs) have shown excellent rates of sustained virologic response (SVR) and good safety profiles in patients with chronic hepatitis C virus (HCV) genotype 1 infection. We aimed to investigate the effectiveness and safety of two oral DAA combination regimens, ombitasvir/paritaprevir/ritonavir plus dasabuvir (OMV/PTV/r + DSV) and ledipasvir/sofosbuvir (LDV/SOF), in a real-world clinical practice.

Methods: Data from HCV genotype 1 patients treated with either OMV/PTV/r + DSV ± ribavirin (RBV) (n = 1567) or LDV/SOF ± RBV (n = 1758) in 35 centers across Spain between April 1, 2015 and February 28, 2016 were recorded in a large national database. Demographic, clinical and virological data were analyzed. Details of serious adverse events (SAEs) were recorded.

Results: The two cohorts were not matched with respect to baseline characteristics and could not be compared directly. The SVR12 rate was 96.8% with OMV/PTVr/DSV ± RBV and 95.8% with LDV/SOF ± RBV. No significant differences were observed in SVR according to HCV subgenotype ($p = 0.321$ [OMV/PTV/r + DSV ± RBV] and $p = 0.174$ [LDV/SOF]) or degree of fibrosis ($p = 0.548$ [OMV/PTV/r/DSV ± RBV] and $p = 0.085$ [LDV/SOF]). Only baseline albumin level was significantly associated with failure to achieve SVR ($p < 0.05$) on multivariate analysis. Rates of SAEs and SAE-associated treatment discontinuation were 5.4% and 1.7%, in the OMV/PTV/r + DSV subcohort and 5.5% and 1.5% in the LDV/SOF subcohort, respectively. Hepatocellular carcinoma (HCC) recurred in 30% of patients with a complete response to therapy for previous HCC. Incident HCC was reported in 0.93%.

Conclusions: In this large cohort of patients managed in the real-world setting in Spain, OMV/PTV/r + DSV and LDV/SOF achieved high rates of SVR12, comparable to those observed in randomized controlled trials, with similarly good safety profiles.

Keywords: Hepatitis C, Chronic; Genotype 1; Ombitasvir; Paritaprevir; Ritonavir; Dasabuvir; Ledipasvir; Sofosbuvir; Real-world; Antiviral agents; Sustained virologic response; Randomized controlled trials.

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Lay summary: In clinical trials, second-generation direct-acting antiviral agents (DAAs) have been shown to cure over 90% of patients chronically infected with the genotype 1 hepatitis C virus and have been better tolerated than previous treatment regimens. However, patients enrolled in clinical trials do not reflect the real patient population encountered in routine practice. The current study, which includes almost 4,000 patients, demonstrates comparable rates of cure with two increasingly used DAA combinations as those observed in the clinical trial environment, confirming that clinical trial findings with DAAs translate into the real-world setting, where patient populations are more diverse and complex.

Introduction

An estimated 130–170 million people globally are chronically infected with the hepatitis C virus (HCV), and are at significant risk of liver disease, cirrhosis and hepatocellular carcinoma (HCC) [1]. Successful treatment leading to a sustained virologic response (SVR) effectively cures HCV infection, significantly reducing the risk of HCV-related complications, liver transplantation, and death [2,3]. Interferon (IFN)-based therapies were associated with treatment-limiting side effects and resulted in SVR rates of 40–50% in patients with HCV genotype 1 infection [4], the most prevalent genotype worldwide [5].

The advent of direct-acting antiviral agent (DAA) therapy has been widely acknowledged as a revolution in the field of HCV infection. In clinical trials, IFN-free regimens using second-generation DAA combinations yield SVR rates above 90% in genotype 1-infected patients. Ledipasvir and sofosbuvir (LDV/SOF) with or without ribavirin (RBV) resulted in SVR rates of 94–99% in treatment-naïve and treatment-experienced genotype 1-infected patients with and without cirrhosis [6–8], including those co-infected with HIV [9]. Similarly high SVR rates were obtained with the combination of ombitasvir plus paritaprevir and ritonavir (OMV/PTV/r) administered with dasabuvir (DSV) with or without RBV [10–16].

Based on data from these and other trials, both LDV/SOF and OMV/PTV/r + DSV regimens were approved by the European Medicines Agency (EMA) for the treatment of HCV genotype 1 infection. Both regimens were included in the National Hepatitis C Plan developed by the Spanish Ministry of Health, launched on April 1 2015, which allowed for increased access to DAAs in prioritized patients, including those with significant liver fibrosis (F2–F4).

Clinical trials include highly selected patient populations. Treatment is closely controlled and patients are well-supported. However, this potentially limits the applicability of results to routine clinical practice, where populations are more complex, more heterogeneous and not so tightly controlled. Real-world data are needed to confirm clinical trial findings and to guide treatment decisions. The objective of this study was to investigate the demographics and clinical characteristics and evaluate the clinical effectiveness and safety of OMV/PTV/r + DSV and LDV/SOF in two independent HCV genotype 1 patient cohorts.

Patients and methods

This was a retrospective, non-interventional, national, multicenter study evaluating antiviral treatment of HCV-infected patients in routine clinical practice. Data were collected through a National Registry (HEPA-C) under the auspices of the Spanish Association for the Study of the Liver (AEEH) and the Networked Biomedical Research Centre for the Study of the Liver and Digestive Diseases in Spain (CIBERehd). Informed consent was obtained in writing from all patients in the registry. The study recorded data from all patients chronically infected with HCV genotypes 1a or 1b undergoing treatment with OMV/PTV/r + DSV ± RBV or LDV/SOF ± RBV in 35 Spanish centers between April 1 and February 28, 2016. No other inclusion or exclusion criteria were specified. Patient follow-up ranged from 24 to 36 weeks depending on-treatment duration. The study was approved in advance by the Research Ethics Committee of Hospital Universitario Puerta de Hierro of Majadahonda (PI18-16; Madrid, Spain).

Treatment

The decision to treat and the choice of treatment, including treatment duration and the use or not of concomitant RBV, was entirely at the discretion of the treating physician. In accordance with the individual Summaries of Product Characteristics (SmPCs) issued by the EMA during the course of the study for each anti-HCV drug, recommended treatment duration and use of RBV was determined by clinical characteristics in individual patients.

Measurements

Demographic, clinical, adverse event and virologic data were collected throughout treatment and the post-treatment follow-up period. HCV RNA levels were determined using either the COBAS® AmpliPrep®/COBAS TaqMan® (Roche Molecular Systems, Pleasanton, CA, USA; lower limit of detection [LLOD] 15 IU/ml) or the m2000SP/m2000RT (Abbott Molecular, Des Moines, IL, USA; LLOD 12 IU/ml) real-time PCR-based assays. Measurements were taken at baseline, weeks 4, 12 and 24 of therapy, and 4 and 12 weeks after treatment completion. Cirrhosis (F4) was defined by transient elastography score >14 kPa, or liver biopsy or clinical evidence of liver decompensation.

Outcomes

Virologic response, defined as undetectable HCV RNA, was assessed at week 4 of treatment (rapid viral response [RVR]), at end of treatment (EOT) and at week 4 (SVR4) and week 12 (SVR12) post-treatment. Virologic failure was defined as detectable HCV RNA at any time during treatment or post-treatment follow-up. Change in renal function was assessed at week 12 post-treatment. Details of all recorded serious adverse events (SAEs) were collected from the time of first drug administration to week 12 after the planned EOT. SAEs were defined as any life-threatening event, an event that led to a hospital admission, prolonged an existing hospital stay or resulted in death, or those that were considered serious based on the judgment of the treating physician. Incident hepatic decompensation was defined as the presence of variceal hemorrhage, ascites, and/or portosystemic (hepatic) encephalopathy. Anemia was defined as a hemoglobin level <10 g/dl.

Statistical methods

Frequencies, numbers and percentages are used for descriptive analysis of categorical variables. Quantitative variables are presented as mean, range and standard deviation (SD). Results were analyzed using the intent-to-treat approach. Efficacy and safety analyses were performed using the X^2 test, Student's t test or the Mann-Whitney U test for comparisons between independent groups. The Fisher's exact test was used when frequencies were less than 5%. Wilcoxon signed-rank test or χ^2 test were used for within group comparisons.

Logistic regression models were used to identify predictive factors for no response and adverse events. Multivariate stepwise logistic regression analysis was used to identify any independent baseline factors predictive of no response or development of adverse events. A range of continuous and categorical variables were tested in the model (Table S1). For each tested covariate, a univariate model was estimated. Covariates with p <0.05 in likelihood ratio testing in univariate analysis were included in a multivariate model, and selection of independent covariates was based on a backward elimination procedure, retaining covariates with p <0.05. Computation for the statistical tests was performed with IBM®