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ORIGINAL RESEARCH

Sustained virological response in patients with HCV treated with daclatasvir plus sofosbuvir, with or without ribavirin: a large, field-practice study

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Abstract

Background: The once-daily oral combination of daclatasvir (DCV) and sofosbuvir (SOF), with or without ribavirin (RBV), is effective and well tolerated in patients with hepatitis C virus (HCV). However, further field-practice studies are necessary to investigate the effectiveness and safety of the DCV+SOF combination in diverse subpopulations of patients with HCV, including those who are more challenging to treat such as patients with a genotype 3 (G3) infection. The aim of this retrospective, multicenter, field-practice study was to investigate the therapeutic efficacy and safety of the oral combination of DCV and SOF, with or without RBV (DCV+SOF±RBV), in a large unselected cohort of patients with chronic HCV infection (CHC).

Patients and methods: Consecutive patients received DCV+SOF±RBV for 12 or 24 weeks. The efficacy endpoint was sustained virological response at 12 weeks after the end of treatment (SVR12). Safety factors were also considered.

Results: A total of 620 patients were included in this study; the predominant genotype was G3 (55.3%). Of the total sample, 248 (40%) patients were treated with DCV+SOF+RBV and 372 (60%) did not receive RBV. The majority of patients assessed at week 12 (98%, 596/608) achieved SVR12. Among G3 patients, 98.8% (335/339) achieved SVR12. The most common adverse event was elevated bilirubin (30.6%), recorded in 4.9% of cases as a grade 3–4 adverse event.

Conclusion: This study shows the high pan-genotypic effectiveness and safety of the DCV+SOF±RBV combination in a large, unselected sample of CHC patients with G1–4, including a wide proportion of G3 CHC patients.

Keywords: daclatasvir, direct-acting antivirals, HCV NS5A inhibitors, HCV replication complex, ribavirin, sofosbuvir.

Citation

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Introduction

The current standard of care for chronic hepatitis C virus (HCV) infection (CHC) is a combination treatment with oral direct-acting antivirals (DAAs).[1,2] DAAs target the HCV viral replication either by directly binding components of the replicase complex or by terminating the RNA chain.[3] The major goals of DAA combination therapy are (1) to inhibit virus replication and (2) to induce clearance of the virus by cellular death of infected cells.[4] The latter is achieved by combining agents targeting different viral molecules. This allows a reduction in the risk of selection of resistant viral strains.[5]

HCV non-structural protein 5A inhibitors are an integral component of DAA combination therapies and include daclatasvir (DCV), ledipasvir, ombitasvir, elbasvir, and velpatasvir. Among these, DCV was the first lead compound.[6] The combination of DCV with sofosbuvir (SOF) – a nucleotide analog HCV RNA polymerase (non-structural protein 5B)[7] inhibitor – has demonstrated pan-genotypic anti-HCV activity.[8]

In phase III studies, the once-daily combination of oral DCV and SOF, with or without ribavirin (RBV), was well tolerated and demonstrated rates of sustained virological response at 12 weeks after the end of treatment (SVR12) exceeding 90% in patients with HCV, including in specific subgroups such as those with advanced fibrosis or cirrhosis,[9,10] HIV/HCV coinfection,[11] HCV recurrence after liver transplant,[12] and patients with genotype 3 (G3) infection.[10]

In addition to clinical trials, several observational analyses have investigated the efficacy and safety of DCV+SOF combinations in a clinical practice setting, thus providing additional information in different unselected populations, with varying severity of liver disease stage or comorbidities.[9–22] However, further field-practice studies are necessary to investigate the effectiveness and safety of the DCV+SOF combination in diverse subpopulations of patients infected with HCV, including those more challenging to treat such as those with G3 infection, for whom only scant evidence exists.[19,23]

The aim of this multicenter, field-practice study was to investigate the therapeutic efficacy and safety of the oral combination of DCV and SOF, with or without RBV (DCV+SOF±RBV), in a large unselected Italian cohort of patients with CHC. Specific data on G3 infection are also presented.

Patients and methods

This retrospective multicenter study involved 21 centers located over various Italian regions. All consecutive patients with CHC who, according to the criteria established by the Italian Medicines Agency (AIFA),[24] were candidates to treatment with DCV+SOF±RBV during the period January 2015 to December 2016 were included. RBV was added according to criteria applied in daily practice, namely Hb values, results of Fibroscan analysis, and failure of previous treatments. The AIFA criteria include CHC patients (any genotype) with cirrhosis (Child score A and B) and/or resected hepatocellular carcinoma, patients with any grade of fibrosis, transplant recipients, candidates to liver transplant, patients with severe extrahepatic manifestations, infected health professionals, patients with renal insufficiency undergoing maintenance hemodialysis treatment, and bone marrow or solid organ (not liver) transplant candidates.

All enrolled patients received oral DCV+SOF±RBV daily for 12 or 24 weeks. According to Summary of Product Characteristics indications, in each center, patients were assessed at baseline, at weeks 4 and 6 (if necessary) during treatment, and at weeks 12 and 24 after treatment completion. The demographic, clinical, and laboratory characteristics of the enrolled patients were recorded at baseline and at all follow-ups. Fibrosis stage was evaluated by transient elastometry (MetavirF3 >10 kPa, F4 >13 kPa). A diagnosis of cirrhosis was made using data obtained from clinical and laboratory tests and instrumental findings. Moreover, cirrhosis was defined by the presence of at least one of the following clinical conditions: decompensation, platelet count <100,000/mm^3, and presence of esophageal varices. HCV-RNA was measured at baseline, during treatment at weeks 2, 4, and 12, and during follow-up at weeks 4 and 12.

The efficacy endpoint was SVR12. SVR12 was defined as HCV-RNA below the assay's lower limit of quantitation (LLOQ) at 12 weeks after the end of treatment. High RNA levels were defined as >10^6 IU/mL. Adverse events (AEs) were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. All patients signed an informed consent for the use of their data for research purposes, and the study was conducted according to the principles of the Declaration of Helsinki and the Italian Personal Data Protection Law. The local Ethical Committees have approved the study design.

Descriptive analysis of clinical characteristics was performed using the SSPS package (v. 20.1).

Results

Baseline characteristics

In total, 620 patients were included in this study. Table 1 shows the patient demographic and clinical characteristics. The mean age at baseline was 60±9 years, and the mean BMI was 24.4 kg/m^2. Most patients were men (63.2%), while 40.5% of patients were non-responders to previous treatments (14.3% were treated with PegIFN2a+RBV, 15.7% with boceprevir or telaprevir plus IFN plus RBV, 10.5% were non-responders to SOF monotherapy).

The predominant genotype was G3 (55.3%), followed by G1 (30%), G2 (11%), and G4 (3.7%). Half of the patients had cirrhosis (50.3%), of whom 150/312 (48.1%) had a Child A score of 5 and the remaining had a Child A score of 6. The model for end-stage liver disease (MELD) score was 8 in 110/312 (35.2%) of patients, 9 in 123/312 (42.3%) of patients, and 10 in the remaining patients. All patients with cirrhosis were

compensated. In total, 245/620 (39.5%) patients had high HCV-RNA baseline levels. Mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels before starting treatment were 89±55 U/L and 101±73 U/L, respectively. Mean albumin was 3.5 g/dL (range 2.8–3.9). A total of 69 (11.2%) patients had HIV coinfection, while 7 (1.1%) patients had hepatitis B virus coinfection.

Treatments and outcomes

Overall, 218 (35.2%) patients received DCV+SOF±RBV treatment daily for 12 weeks (34.8% of those with G3 infection), while 392 (63.2%) received treatment for 24 weeks. No differences in the frequency of the two treatment schemes across patients infected with different genotypes were reported; the decision to treat with either scheme was based upon the specific clinical status of each patient. Of the total sample, 248 (40%) patients were treated with DCV+SOF plus RBV (43.2% of those with G3 infection). Again, no differences across patients infected with different genotypes were reported.

Of the 608 patients assessed at week 12 (12 were lost to follow-up), the majority of patients (52.5%) reached HCV-RNA levels below LLOQ at week 4, while 18.8% of patients reached HCV-RNA levels below LLOQ at the end of treatment. The majority of patients assessed at week 12 (98%, 596/608) achieved SVR12. Furthermore, 100% of patients with CHC G1 and G4 achieved SVR12, 87.7% (58/66) of patients with CHC G2 achieved SVR12, and 98.8% (335/339) of patients with G3 CHC achieved SVR12. SVR12 was also confirmed at 24 and 48 weeks, in all cases. At an additional 6-month follow-up (1.5 years after the end of treatment), no cases of recurrence were reported.

At week 12, mean AST and ALT levels were 26±15 U/L and 27±17 U/L, respectively.

With reference to treatment failure, 12/608 (2%) patients did not achieve SVR12. Of these, 8 were G2 CHC patients, previously treated with SOF+RBV. Among G3 patients with treatment failure, 4 were naive to treatment (two with HIV coinfection). All patients with virological failure (*n*=12) had cirrhosis. All patients with treatment failure had been treated with DCV+SOF plus RBV for 24 weeks.

Safety analysis

Overall, 46% of patients reported at least one AE that was related to treatment (Table 2). The most common AE was elevated bilirubin (30.6%), recorded as a grade 3–4 AE in 4.9% of cases. Anemia was frequent (mean Hb 8.2±3.4 g/dL), particularly among patients treated with RBV: 27.0% *versus* 18.3% among patients not treated with RBV (explorative $p<0.05$, χ^2 test). Patients not on RBV developed anemia, likely due to malnutrition. No cases of decompensation or major complications were reported in cirrhotic patients (encephalopathy, ascites).

Table 1. Patient characteristics at baseline (*n*=620).

Patient characteristics	Value
Age (years), mean (SD)	60 (9)
Men, *n* (%)	392 (63.2)
BMI, mean (SD)	24.4 (4)
Naive to treatment, *n* (%)	251 (40.5)
HCV genotype, *n* (%):	
– Genotype 1	186 (30.0)
– Genotype 2	68 (11.0)
– Genotype 3	343 (55.3)
– Genotype 4	23 (3.7)
HCV RNA >2 × 10^6 IU/mL, *n* (%)	245 (39.5)
Cirrhosis, *n* (%)	312 (50.3)
Fibrosis stage F4, *n* (%)	443 (71.5)
ALT (U/L), mean (SD)	86 (55)
AST (U/L), mean (SD)	101 (73)
Coinfection with HIV, *n* (%)	69 (11.2)
Coinfection with HBV, *n* (%)	7 (1.1)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HBV, hepatitis B virus; SD, standard deviation.

Table 2. Treatment-related adverse events (*n*=620).

Treatment-related AEs	*n*	%
At least one AE	280	46.0
Elevated bilirubin	190	30.6
Elevated bilirubin grade 3–4	30	4.9
Anemia:		
– Patients treated with RBV (*n*=248)	67	27.0
– Patients not treated with RBV (*n*=372)	68	18.3

AE, adverse event; RBV, ribavirin.

Discussion

Herein, we evaluated the real-world effectiveness of the once-daily oral combination of DCV+SOF±RBV. Our starting population included 620 CHC G1–4 patients yet 12 patients were lost to follow-up at week 12 (608 patients were available for data collection). Among the studied subjects, 50.3% had cirrhosis and almost 60% had received previous anti-HCV treatment. The studied regimens were administered for at least 12 weeks in patients with HCV G1, G2, G3, and G4 infections. Of note, we did not include patients with decompensated cirrhosis, who would be the most challenging to treat.

In the analyzed population, 98% of patients reached SVR12, while 12 (2%) patients had virological failure. These findings

confirm the high pan-genotypic effectiveness of the studied combination in patients with advanced liver disease, as shown in other studies,[9–16] attributed to the mechanism of action characterized by the direct inhibition of viral replication. Given the high rate of treatment success, we were not able to investigate the potential predictive factors.

Remarkably, compared with other real-world studies,[17,18] our cohort included a higher number of G3 patients (*n*=343, 55.3%), who are more challenging to treat in clinical practice.[23] According to recent estimates,[25] G3 is the second most prevalent HCV genotype worldwide: it is estimated that HCV G3 accounts for 30.1% of cases globally, corresponding to 54.3 million people. Approximately three-quarters of G3 HCV occurs in south Asia, where 71.6% of infections are attributable to G3. Infection with G3 HCV has been associated with an increased risk of development of steatosis or hepatocellular carcinoma as well as with progression to cirrhosis compared with other HCV genotypes.[26,27]

In our study, 98.8% of G3 CHC patients reached SVR12. The four G3 patients who experienced virological failure were cirrhotic (Child A score of 6). These findings are comparable with those obtained in the phase III ALLY-3 study,[10] which included 152 patients with G3 HCV and in which a 12-week regimen of DCV plus SOF achieved SVR12 in 96% of G3 patients without cirrhosis but only in 63% of patients with cirrhosis. Of note, in patients with advanced fibrosis or compensated cirrhosis, the addition of RBV to the regimen for 12 or 16 weeks increased SVR12 rates to 83% and 89%, respectively.[10]

Before the approval of DCV, a compassionate use program[14] was established in Europe to grant early access to DCV in combination with SOF, with or without RBV, for patients with CHC infection who urgently required treatment and were without therapeutic alternatives. In this study, SVR12 was achieved by 88% (82/93) of patients with G3 infection, including 88% among those treated with DCV+SOF and 89% of those treated with DCV+SOF+RBV.[14]

Understanding the effectiveness of anti-viral regimens in real-world settings is essential to provide practical information and adopt better HCV treatment decisions.[28,29] Herein, we considered a large sample of patients – with a wide range of baseline disease characteristics – that were treated in a real-world clinical setting, therefore allowing us to evaluate an unselected population of patients, some of whom may not have been included in clinical trials. However, our study presents all the limitations of any retrospective analysis conducted on consecutive patients (e.g. poor reporting of data).

The treatment scenario for HCV has undergone major progress in the last years, with the introduction of new effective therapeutic regimens. Therefore, the DCV+SOF combination is no longer marketed in Europe and the USA.[30,31] However, according to our results and other evidence, we believe that there is still room for the DCV+SOF combination in clinical practice. In particular, this therapeutic regimen may have a major role in less economically developed countries, wherein HCV patients are not treated or receive poorly effective therapies.

The strengths of our study include the large sample, its focus on G3 infection and its real-life nature. Nevertheless, it is limited due to being a retrospective analysis, although it was conducted on consecutive patients.

Conclusion

Our study demonstrates the high pan-genotypic effectiveness and safety of the DCV+SOF±RBV combination in a large, unselected cohort of CHC patients with G1–G4, which includes a wide proportion of G3 CHC patients.

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