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Efficacy of sofosbuvir-based therapy in Sardinian patients: a real-life situation case study

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ABSTRACT:

— ***Objective:*** The Hepatitis C Virus (HCV) is a RNA-virus of the Flavivirus family that infects the liver causing cirrhosis, liver failure, and hepatocellular carcinoma, after a few years. The aim of this retrospective study was to analyze the efficacy and safety of sofosbuvir-based therapy in Sardinian patients for the treatment of HCV infections.

— ***Patients and Methods:*** Ninety-six patients were treated during the study period. The genotype and plasma levels of the virus were determined with the instruments available at the internal analysis laboratory within the University Hospital of Sassari (Sassari, Italy).

— ***Results:*** The results obtained demonstrate the excellent tolerability and good efficacy of sofosbuvir-based therapy in fighting against HCV infections.

— ***Discussion:*** The analysis of the results highlighted the therapeutic innovation brought by the second generation of direct-acting antiviral (DAA) agents witchers, with less side effects, as well as the possibility of receiving exclusively oral therapy, also allowing high adherence to the therapy.

— ***Keywords:*** HCV, Sofosbuvir, Real-life, Efficacy, SVR.

INTRODUCTION

The Hepatitis C Virus (HCV) is a RNA-virus of the Flavivirus family, characterized by a genome composed ofa single strand of RNA that encodes for three structural proteins (C, E1 and E2) and seven non-structural proteins (NS1, NS2, NS3, NS4A, NS4B, NS5A and NS5B), necessary for the replication cycle of the virus[1,2]. The sequence of the HCV genome is highly variable: multiple viral genotypes have been identified[3] and have shown to respond differently to treatment[4]. At the end of 2014, in Italy, other active ingredients were added to the first drugs used in the treatment of HCV (i.e. Interferon Alpha-2, ribavirin, boceprevir and telaprevir). Certain ingredients, such as paritaprevir and simeprevir (NS3/4A protease inhibitors), sofosbuvir and dasabuvir (NS5B RNA polymerase inhibitors), and daclatasvir, ledipasvir and ombitasvir (NS5A inhibitors) were added alone or in fixed combinations. Among these drugs the most prescribed was sofosbuvir, which was shown to be highly effective[5,6]. The aim of this retrospective study is to analyze the efficacy and safety of sofosbuvir-based therapy in a mono-centric "real-life"setting with respect to a sustained virologic response (SVR) in Sardinian patients.

PATIENTS AND METHODS

In this retrospective study we analyzed ninety-six patients with different genotypes of HCV-infection, who were treated with sofosbuvir-based therapy, from February to December 2015, and followed up at the University Hospital of Sassari (Sassari, Sardinia, Italy). The inclu-

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Table 1. Distribution of patients by age.

Age	Female (n = 34)	Male (n = 62)
Age < 50	4	13
Age 50 - 59	6	29
Age 60 - 69	9	7
Age 70 - 79	13	11
Age > 79	2	2
Averageage	**65,14 ± 10,51**	**58,07 ± 11,44**

Table 3. Distribution of patients based on previous treatments.

Previous treatments	Null Responder	Partial Responder	Relapser	Total
IFN	1		2	**3**
PEG-IFN+RIBA	24	4	14	**42**
PEG-IFN+RIBA +DAA 1° GEN	5	1	2	**8**
Total	**30**	**5**	**18**	**53**

sion criteria were as previously defined by the Italian Medicines Agency (AIFA)[7]. The qualitative detection of the antibody anti-HCV was performed with the ORTHO HCV Version 3.0 ELISA Test System (Ortho-Clinica Diagnostics, Raritan, NJ, USA). The plasma HCV RNA levels obtained were further measured using the COBAS® TaqMan® Analyzer (Roche Molecular Systems, Pleasanton, CA, USA). The final HCV genotype was identified using the Versant™ HCV Genotype 2.0 (Siemens Healthineers, Erlangen, Germany) and the fibrosis of the liver was measured with the FibroScan system. Medical records were used to analyze the efficacy of the therapy and any indication of adverse events.

RESULTS

As shown in Table 1, patients who participated in this study were predominantly males (n = 62; 64.6%) and only 34 (35.4%) were females; however, the average age of women was higher than that of men (65.1 *vs.* 58.1 years). Most patients were characterized by the HCV genotype 1 (n = 52; 54.2%), ande were further divided in 14 patients with HCV type 1A and 38 patients with HCV type 1B (Table 2). The HCV genotype 1 was followed by genotypes 3 and 4, which were found to be equally frequent in our sample population (n= 20 for each genotype, 20.8% each). Finally, only 4 patients (4.2%) were characterized by the HCV genotype 2. In accordance with the criteria established by AIFA in terms of access to therapy, according to which priority to treatment at the early stages should be given to the sickest patients, we found that most of the patients (n = 78, 81.3%) of our dataset presented a F4 fibroscan (Table 2). Fifteen patients (15.6%) presented a F3 fibroscan, only one patient an F2 fibroscan, while 2 patients were not evaluated (N/A) (Table 2). All the patients with a F4 fibroscan expressed fully blown cirrhosis. Six patients (of which five with a F4 fibroscan and one with a F3 fibroscan) developed a hepatocellular carcinoma (HCC). Fifty-three patients (out of 96) were previously treated with interferon + ribavirin, which is associated, in some cases, to first generation DAA. Of these, thirty patients (56.6%) were non-responders, five (9.4%) were partial responders and eighteen (34%) relapsed (Table 3). The other forty-three patients of our sample were never exposed to treatment. As shown in Table 4, the most commonly used therapy was SOF+SIM+RIBA (38.5%), followed by SOF+RIBA (25%) and DAC+SOF+RIBA (18.8%). The first of the three was shown to be the preferred treatment in cases of infections by HCV genotype 1B (n = 19; 50%) and genotype 4 (n = 13; 65%), while the second therapy with DAC+SOF+RIBA was more effective for the treatment of HCV genotype 1A (n = 6; 42.9%). SOF+RIBA, finally, was the most common therapy in patients characterized by HCV genotype 3 (n = 13; 65%) and the only treatment used for genotype 2. In terms of duration of therapy (Table 5a, top panel), we observed that 51 patients performed a 12-week treatment and 45 a 24-week treatment. In the first group, most of the patients suffered from HCV Genotype 1B (n = 27; 52.9%) and genotype 4 (n = 15; 29.4%), while in the second group a major cause of infection was found to be related to genotype 3 (n = 19; 42.2%) followed by genotype 1B (n = 11; 24.4%). Despite the obvious impossibility of establishing with certainty that patients actually took each dose of medicine prescribed, all of them showed up for the verification visits. Also, the duration of therapy appeared to be related to the therapeutic treatment adopted (Table 5b, bottom panel). In fact, most of the patients who followed a 12-week treatment (n = 36; 70.6%) were treated with the association SOF+SIM+RIBA, which, as previously described, was the most effective treatment in cases of infections by HCV genotype 1B and 4. The same consideration was observed in 24-week therapies where SOF+RIBA was the treatment most commonly

Table 2. Distribution of patients by HCV virus genotype and liver conditions.

Fibroscan	Cirrhosis	HCV Genotype 1A	HCV Genotype 1B	HCV Genotype 2	HCV Genotype 3	HCV Genotype 4
F2	NO	1				
F3	NO	2	8	1		4
F4	YES	11	30	3	20	14
#N/A	#N/A					2
Total by genotype		**14**	**38**	**4**	**20**	**20**

Table 4. Therapeutic choice by HCV genotype.

Fibroscan	HCV Genotype 1A	HCV Genotype 1B	HCV Genotype 2	HCV Genotype 3	HCV Genotype 4	Total
DAC+SOF	1	1		2	1	**5**
DAC+SOF+RIBA	6	8		4		**18**
HARV+RIBA		3				**3**
SOF+SIM	2	3			2	**7**
SOF+SIM+PEGIFN+RIBA		1				**1**
SOF+SIM+RIBA	5	19			13	**37**
SOF+PEGIFN+RIBA				1		**1**
SOF+RIBA		3	4	13	4	**24**
Total	**14**	**38**	**4**	**20**	**20**	**96**

DAC = daclatasvir; HARV = ledipasvir + sofosbuvir; PEGINF = pegylated interferon alfa-2a; RIBA = ribavirin; SIM = simeprevir; SOF = sofosbuvir.

Table 5. Duration of therapy byinfecting genotype (a, top panel) and therapeutic treatment (b, bottom panel).

	12 Weeks	24 Weeks	
a) ***Genotype***			
HCV Genotype 1A	7	7	**14**
HCV Genotype 1B	27	11	**38**
HCV Genotype 2	1	3	**4**
HCV Genotype 3	1	19	**20**
HCV Genotype 4	15	5	**20**
	51	**45**	**96**
b) ***Therapy***			
DAC+SOF		5	**5**
DAC+SOF+RIBA	3	15	**18**
HARV+RIBA	2	1	**3**
SOF+SIM	7		**7**
SOF+SIM+PEGIFN+RIBA	1		**1**
SOF+SIM+RIBA	36	1	**37**
SOF+PEGIFN+RIBA	1		**1**
SOF+RIBA	1	23	**24**
Total	**51**	**45**	**96**

used (n = 23; 51.1%) for genotype 3. In terms of therapy outcome (Table 6), almost all of the patients (n = 88) obtained a therapeutic success at the end of therapy (EOT), independently from the viral genotype infection. Six patients experienced a relapse mainly due to HCV genotype 3 (50%). The single patient who did not respond to therapy was also infected by genotype 3. Unfortunately, only two people presented long-term follow-ups (12 and 20 months). Finally, no adverse reactions were recorded in our sample population during the study period.

DISCUSSION

As previously demonstrated, free interferon treatments, based on new drugs acting directly on HCV, have numerous advantages over therapy containing interfero[8], such as fewer side effects and a greater efficacy. The effectiveness of the other therapies oscillated from 30-70% (the results observed were highly variable, depending on the study[9,10], as opposed to SVR whose efficacy was shown to be around 90% for therapies based on sofosbuvir[11]. As reported, another important advantage of the new DAA treatment is the possibility to select the most appropriate therapy based on the infecting genotype[12] in order to obtain the total eradication of the pathogen, reducing the need to resort to a therapy against hepatocellular carcinoma and/or liver transplantation.

CONCLUSIONS

As shown in our work, numerous advances have been made in the treatment of HCV infections, which, togeth-

Table 6. Therapy outcome by genotype.

Outcome	HCV Genotype 1A	HCV Genotype 1B	HCV Genotype 2	HCV Genotype 3	HCV Genotype 4	Total for outcome
DEMISE		1				1
NULL RESPONDER				1		1
RELAPSER	2			3	1	6
EOT	6	11		5	7	29
SVR 1 MONTH	1	2		3	1	7
SVR 3 MONTHS	4	11	1	4		20
SVR 6 MONTHS	1	13	2	4	10	30
SVR 12 MONTHS					1	1
SVR 20 MONTHS			1			1
Total by genotype	**14**	**38**	**4**	**20**	**20**	**96**

EOT: end of therapy; SVR: sustained virologic response.

er with an increate attention in implementing risk-oriented health care facilities (e.g. blood transfusions), can contribute to the control of the disease. The total colonization of the virus is probably still utopian at this stage, in spite of the high prevalence and number of cases of transmission that, however, do no reach the attention of the health system[13].

Conflict of Interests:
The Authors declare they have no conflict of interest.

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