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Consensus

Treatment of Hepatitis C virus infection in Italy: A consensus report from an expert panel

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ABSTRACT

Hepatitis C virus (HCV) infection remains one of the main causes of chronic liver disease worldwide. The advent of direct-acting antivirals (DAAs) has significantly improved the course of patients with chronic HCV infection (CHC), due to the ability of these drugs to achieve high rates of sustained virological response (SVR). These exceedingly high rates of SVR and the excellent safety data have been confirmed in real life practice. Evolving guidelines have been issued by national and international scientific societies in accordance with the progression of clinical knowledge and the availability of new DAAs. These recommendations, however, may not be applied universally because of delays in drugs reimbursability in different countries and because some National Health Systems identify only patients with advanced disease as a treatment priority. Italy in this regard is a prototype about DAAs treatment of CHC patients.

With the aim to assess the Italian treatment experience with DAAs and to respond to unmet needs in treatment optimization of antiviral therapy in specific settings of CHC patients, a group of Italian experts met in Stresa in February 2017. The summary of the considerations arising from this two-day meeting and some statements regarding a few open issues are reported in this position paper.

1. The HCV treatment scenario in Italy

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide and is responsible for a large proportion of liver-related deaths, mostly because of hepatocellular carcinoma (HCC) and cirrhosis [1,2].

Approximately 180 million people worldwide are currently infected with HCV, although reliable epidemiological data are elusive because of the asymptomatic nature of the infection and the lack of screening programs in most countries [3,4]. Even in Italy the exact number of HCV-positive patients is unknown, however it is believed that there is a large proportion of CHC patients (roughly 1%), most with age >60 years with advanced liver disease, with nearly 80,000 cirrhotics and at least 3000 with decompensated disease. On the other hand a reliable assessment of the impact of the infection is represented by the number of patients transplanted due to HCV (500/year) and by deaths caused by the virus (about 10,000/year).

Until the end of February 2017, 68,270 HCV patients had been treated with DAAs (http://www.agenziafarmaco.gov.it/content/aggiornamento-epatite-c). According to the AIFA rules only patients with most advanced liver disease, cured HCC, listed for liver transplant (LT), with HCV recurrence after LT or after transplant of solid organ other than liver, and with severe HCV-related extra-hepatic manifestations (EHMs) could be considered for the DAAs treatment. The treated patients were: 43,453 (64%) cirrhotics with or without HCC (cured with surgical or loco-regional therapies); 18,497 (27%) METAVIR fibrosis score F3; 3191 (4%) with severe EHMs, i.e. cryoglobulinemic syndrome with organ damage or B-cell lymphoproliferative syndromes; 1908 (3%) with post-LT recurrence, 620 (1%) METAVIR F0-F2 who underwent

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pegylated interferon (Peg-IFN) + Ribavirin (Rbv) + simeprevir (SIM) treatment; 309 (0,5%) listed for LT with cirrhosis MELD <25 and/or HCC within the Milan criteria with the possibility of waiting in a list of at least 2 months and 292 (0.5%) with CHC and non liver solid organ transplantation or bone marrow transplantation.

Based on the Italian National Health System the reimbursability of DAAs was therefore granted according to urgency of treatment, without the possibility to use these drugs in patients with less advanced fibrosis (F0–F2). Moreover the price of DAAs was negotiated centrally with price/volume agreements and pay-per-patient reimbursement, regardless of treatment duration with a cost per patient of nearly 6000–10,000 euro. These methods of reimbursement have allowed using DAAs longer without the need to identify the patients being treated for shorter time to save costs.

2. The near future scenario of HCV treatment

Although in Italy the treatment was initially reserved exclusively to patients with advanced liver disease, in the last months of 2016 the percentage of F3 patients undergoing DAAs gradually increased up to reaching the number of F4 patients, to indicate that treatment indication is moving toward lesser stages of disease. Recently it has been estimated that are still present at least 100,000–150,000 F0–F3 and 10,000 F4 patients that need antiviral treatment. These patients in the next four years might all be treated with an annual cost of 400 million euros. The progressive decline of patients with urgency of treatment will allow in the short term to expand treatment criteria without, however, bear the cure for all infected patients. Unfortunately our country lacks of a plan for universal or targeted screening of infected patients; as well as of a strategy for retreatment of patients who previously failed DAAs, and a wide access to DAAs treatment for people at high risk of viral transmission (i.e. women of childbearing age who wish to become pregnant; healthcare professional; people with sexually transmitted diseases; prisoners; people who inject drugs).

Treatment of CHC has been revolutionized in the last few years by the introduction of highly effective and well tolerated DAAs able to achieve >90% rates of SVR in many groups of patients including those with more advanced liver disease. Successful anti-HCV treatment can stop liver disease progression eventually reducing both liver-related and overall mortality [5,6].

The second wave of DAAs has significantly improved SVR rates, moreover these drugs are better tolerated and have more convenient once-daily dosing regimens with shorter treatment schedules, i.e. 12 weeks in the majority of patients and in selected ones only 8 weeks.

The future combination regimens with new generation oral agents may further increase SVR rates without the need for Rbv, with shorter treatment durations and with more favorable tolerability profiles. With these treatments we might finally have the potential to treat the infection and not just the disease, with the aim to eradicate HCV worldwide.

However, also with these new DAAs some types of patients will remain “difficult to treat”, such as: DAAs-experienced patients with resistance associated variants (RAVs); patients with decompensated cirrhosis, and genotype 3 cirrhotic patients.

During the last AASLD 2016 meeting, several new DAAs regimens were presented. The combination of sofosbuvir (SOF)/velpatasvir (VEL) with the new pangenotypic HCV NS3/4A protease inhibitor (PI) Voxilaprevir (VOX) is one of the new a fixed-dose formulations. The POLARIS-2 study compared treatment with SOF/VEL/VOX for 8 weeks to SOF/VEL for 12 weeks in genotype 1–6 patients with and without compensated cirrhosis who have not previously received treatment with DAAs. Patients with genotype 3 infection and cirrhosis were excluded from this study, but included in the POLARIS-3 study. Eight weeks of SOF/VEL/VOX achieved 95% SVR rates compared to 98% with the 12 week SOF/VEL regimen. The SVR rates with SOF/VEL/VOX and SOF/VEL were 91% vs 99% and 96% vs 98% in patients with and without cirrhosis, respectively. Higher relapse rates were reported in the 8 weeks treatment arm particularly in genotype 1a patients [7]. POLARIS-4 study compared 12 weeks of SOF/VEL/VOX with SOF/VEL in 182 and 151 patients, respectively, with previous failure of non-NS5A containing DAA regimens. SVR rates were higher among patients treated with SOF/VEL/VOX compared to SOF/VEL (97% vs 90%) [8].

In the randomized, open label, multicenter ENDURANCE-1 study, 703 naïve or treatment-experienced (prior IFN ± Rbv or SOF + Rbv ± IFN) genotype 1 patients without cirrhosis or with HIV co-infection were treated for either 8 or 12 weeks with the combination of pangenotipic NS3/4A PI Glecaprevir (GLE) and pangenotipic NS5A inhibitor Pibrentasvir (PIB) [9]. Both arms showed high rates of SVR: 99% and 100%, respectively. The same high SVR rate (99%) was also reported in the ENDURANCE-4 trial, that investigated the safety and efficacy of a 12-week GLE/PIB treatment in 121 non cirrhotic patients infected with HCV genotype 4-6, either naïve or treatment-experienced (prior IFN ± Rbv or SOF + Rbv ± IFN) [10], and also in the ENDURANCE-2 trial, that investigated the safety and efficacy of a 12-week GLE/PIB treatment in 302 naïve or treatment-experienced (prior IFN ± Rbv or SOF + Rbv ± IFN) non cirrhotic genotype 2 patients [11].

The SURVEYOR-II, Part 3 study evaluated the efficacy and safety of GLE/PIB for 12 or 16 weeks in 131 CHC patients genotype 3 with or without cirrhosis including those with prior treatment-experience [12]. In experienced cirrhotic patients, 16 weeks of GLE/PIB achieved 96% of SVR compared to 98% of naïve patients treated for 12 weeks, whereas in treatment-experienced non cirrhotic patients, 16 weeks achieved 96% of SVR vs 91% in those treated for 12 weeks.

The EXPEDITION-IV study reported 98% SVR rate in 104 genotype 1–6 patients with severe renal impairment (82% on hemodialysis) treated with 12 weeks of GLE/PIB [13]. This is a promising study, since the DAAs recommended to date for treatment of HCV in patients with advanced renal insufficiency are predominantly active in genotypes 1 and 4, whereas genotypes 2 and 3 patients with end-stage renal disease have little chance of treatment.

An interesting new fixed-dose triplet is the pangenotypic MK3 combination, that includes the NS5B polymerase nucleotide inhibitor uprifosbuvir (formerly MK-3682), the already-registered NS3/4A PI Grazoprevir (GZR) and the next-generation NS5A inhibitor Ruzasvir (RZR). The C-CREST trial evaluated the safety and efficacy of the MK3 regimen, with or without Rbv, in 664 genotype 1–3 patients with and without cirrhosis [14]. Genotype 1 patients were randomized to 8 or 12 weeks of the triplet; genotype 2 treatment-naïve patients were randomized to 8 or 12 weeks of the triplet, with or without Rbv, and compared with 16 weeks of only MK3; genotype 3 treatment-naïve and experienced patients were randomized to 8 vs 12 vs 16 weeks, with or without Rbv. MK3 for 8 or 12 weeks achieved 93% vs 98% SVR rates in genotype 1a, and 98% vs 100% SVR rate in genotype 1b patients. In genotype 2 treatment-naïve patients, SVR rates were 86%, 97% and 100% in the 8, 12 and 16 weeks arms, respectively. In genotype 3, MK3 regimen showed 95%, 97% and 96% of SVR in the 8, 12 or 16 weeks arms of treatment. The C-SURGE study evaluated the safety and efficacy of the MK3 regimen in patients who relapsed after LDV/SOF or elbasvir (EBR)/GZR treatment. Eight weeks after the end of treatment, the SVR rates were 98% and 100% in patients randomized to receive 16 weeks MK3 + Rbv or 24 weeks of MK3 without Rbv, respectively [15].