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FROM CURRENT STATUS TO OPTIMIZATION OF HCV TREATMENT: RECOMMENDATIONS FROM AN EXPERT PANEL

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ABSTRACT

Chronic hepatitis C virus (HCV) infection is a major public health problem at a global level, causing an enormous burden of hepatic and extra-hepatic morbidity and mortality. Treatment of chronic HCV (CHC) has been revolutionized in the last few years by the introduction of highly effective and well tolerated direct acting antiviral agents (DAAs) able to achieve > 90% rates of sustained virological response (SVR) in many groups of patients, including those previously excluded from interferon-based regimens. For such reason interferon-free regimens are now the treatments of choice for all patients. Successful anti-HCV treatment can stop liver disease progression and can solve the HCV-related extra hepatic manifestations, eventually reducing both liver-related and overall mortality.

Together with the rapidly accumulating data about the evolution of treatment landscape, different guidelines from national and international Liver Scientific Societies have been published until today. However, these recommendations may not be applied worldwide as, due to high treatment costs, most of them identify as priority groups only patients with advanced liver disease. Moreover some types of patients pose clinical management problems for which even the guidelines do not always provide useful answers.

With the aim of treatment optimization by filling some of the gaps of the current guidelines and addressing the remaining unmet needs in practice, a group of Italian experts, experienced on treatment of HCV infection, met in Stresa in February 2016. The summary of all the considerations arising from this two-day meeting and the final statements are reported in this position paper.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major health problem worldwide and is responsible for a large proportion of liver-related deaths, mostly because of HCV-associated hepatocellular carcinoma (HCC) and cirrhosis (1). However, HCV infection is a many-sided disease able to affect organs other than the liver, causing extra hepatic manifestations with significant morbidity and also significant rates of deaths related to the extra hepatic involvement (2,3).

Approximately 180 million people worldwide (~3% of the population) are currently infected with HCV. Prevalence varies by region, ranging from to 0.1% to 20%, but reliable epidemiological data are elusive because of the asymptomatic nature of HCV and the lack of screening programs in most Countries (4-6). As a result, many unaware HCV-infected individuals remain reservoirs for further transmission and frequently progress to advanced fibrosis, cirrhosis and HCC (1). Even in Italy the number of HCV-positive patients is unknown, although recently it has been estimated that are still present 160-180 thousands chronic hepatitis C (CHC) patients that need antiviral treatment (Epac Onlus – www.epac.it). It must also be noted that Italy is among the countries with the highest prevalence of HCV infection in the HIV-infected population, with an estimated proportion approaching 40%.

Identifying all HCV-infected people is not a trivial point, as, with the launch of direct acting antiviral drugs (DAAs) with very high rates of sustained virological response (SVR), we can significantly modify the natural history of this disease and prevent HCV transmission and/or re-infection. Moreover with these all-oral, highly effective and well tolerated drugs we can potentially treat all patients, including those previously excluded from interferon (IFN)-based

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regimens due to a more advanced liver disease and/or contraindication, those who failed an IFN-based treatment and elderly patients.

However, the cost of such drugs has led many government Health Agencies to identify only some categories of patients as priority. According to the rules of the Italian National Health System, almost 36.000 HCV-infected patients with most advanced liver disease, cured HCC, listed for liver transplant (LT) or with post-LT recurrence, with non-Hodgkin lymphoma (NHL) or mixed cryoglobulinemic syndrome (MCS) have been treated with all-oral DAAs by February 2016.

While the rapidly accumulating new evidences with the use of DAAs, the American (AASLD), the European (EASL) and the Italian (AISF) liver societies have published their own guidelines, with the aim to help clinicians in the optimal management of patients with HCV infection (7-9). Notwithstanding, some unmet needs still exist and some groups of patients pose clinical management doubts for which even the guidelines do not provide answers.

With the aim to fill the gaps of these guidelines and to respond to unmet needs on treatment optimization, a group of Italian experts met in Stresa in February 2016. The summary of the considerations arising from this two-day meeting and some statements for a few open issues are reported in this position paper.

Whom to treat?

The primary goal of HCV therapy is to cure the infection. SVR in patients without cirrhosis or extrahepatic advanced disease is generally associated with the resolution of liver disease and can reduce the HCV-related extra-hepatic disease burden, i.e. diabetes, kidney impairment, lymphoproliferative disorders (LPD) and cardiovascular complications, ultimately leading to an increased survival (2,3,7-15). Cirrhotic patients who achieve SVR may have liver fibrosis regression,

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and reduced risk of hepatic decompensation and portal hypertension complications although they maintain a residual risk of HCC (16-20). Decompensated patients achieving SVR may have a MELD and Child Pugh (CP) score improvement with better survival and some patients waiting for LT may be delisted, although the clinical benefit of treating patients with end-stage liver disease is still poorly known (21).

The combined use of DAAs with or without ribavirin (Rbv) achieves the highest SVR rate (between 95% and 100%) in naïve non cirrhotic patients, but some subgroups of patients with decompensated cirrhosis and compensated genotype 3 cirrhosis have lower response rates (22-26).

Considering all the above mentioned goals of treatment we can make some considerations on the access to DAAs treatments.

Statements

- There is compelling evidence to recommend treatment of all HCV-infected patients.

- Treatment benefit is a measure for relative urgency of treatment, but cannot be used to exclude patients from therapy at any stage of the disease.

- There are categories of patients in whom for medical, social or public health reasons treatment should not be deferred. Any condition in which HCV infection causes social or regulatory discrimination should confer priority of treatment.

  o Co-morbid conditions in which HCV infection alter significantly the management of the diseases should be prioritized for HCV eradication.

  o Patients with advanced fibrosis.

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- o Patients with post-LT HCV recurrent.

- o All non-liver transplanted patients regardless of the staging of fibrosis.

- o Any co-morbidity or viral features associated with worse hepatic or non hepatic prognosis in which a SVR has been linked with improved survival should be considered for treatment: HIV or HBV co-infection; NHL; MCS; non cryoglobulinemic glomerulonephrytis; hematologycal alterations (i.e. trombocytopenia, leucopenia, hemolytical anemia) unrelated to portal hypertension; HCV-3; diabetes; metabolic syndrome; iron storage diseases; cholestatic or autoimmune liver diseases; polyneuropathy.

- Treatment should not be deferred in people at high risk of viral transmission: women of childbearing age who wish to become pregnant; healthcare and other workers involved in chains of potential HCV transmission; people with sexually transmitted diseases; people who inject drugs or on opioid substitution therapy.

Assessment of HCV genotype

Some DAA-based regimens are still genotype dependent, so that a precise and definite assessment of HCV genotype and subtype is mandatory in order to avoid mistreating during the first DAA course. This issue is not trivial, as, in many patients, HCV genotype and subtype have been determined at the beginning of clinical history, often using old-generation tests: indeed for example the commercial assay INNO-LIPA version 1.0 was at higher risk of misclassifying the HCV-1a subtype (27), that nowadays requires in most DAA regimens addition of Rbv or treatment extension. The currently available second-generation commercial assays for HCV genotype show

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instead good concordance (around 90%) with genotype assessment performed by HCV sequencing in the NS5B, or NS3, or NS5A region (28), and are now considered the standard of care for HCV genotyping, so that HCV sequencing is not routinely recommended. However, HCV sequencing can be useful in those rare cases where genotype cannot be determined by the commercial assays (such as cases of mixed infection, or undeterminate, or genotype 1 without subtype information). Moreover, HCV-sequencing along with the precise subtype/genotype assignment, allows the evaluation of drug-resistance (either natural or derived from previous DAA-treatments), thus reducing the risk of failure, especially in difficult-to-treat patients. The relatively low cost of sequencing (compared to therapy) should encourage studies aimed at better defining the advantage of its use at therapy baseline.

Statements

- Accurate assessment of HCV genotype and subtype in genotype 1 by a II generation commercial assay is mandatory before starting a DAA-based treatment.
- HCV sequencing is recommended in all rare cases where genotype or subtype cannot be determined by the commercial assays. Moreover, sequencing provides viral polymorphism information possibly helpful to study the RAVs.

Treatment of patients with HCV-3 infection

HCV genotype 3 is the second most prevalent genotype worldwide, accounting for ~30% of all patients infected with HCV (6). HCV genotype 3 has emerged as a particularly difficult to treat genotype, as all the newly available DAAs have limited anti-HCV-3 activity, thus limiting treatment choices in this patient group. For these reasons HCV-3 remains one of the main topics to address

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in terms of treatment optimization. As HCV-3 has been associated with faster fibrosis progression and an increased risk of liver-related complications (29), this genotype should be regarded as a subset of patients where treatment needs to be prioritized. The peculiar role of HCV-3 in disease progression could be partially explained considering that, due to epidemiological reasons, infection with HCV-3 is endemic in a patient population enriched of high-risk behaviors, like intravenous drug use and concurrent alcohol abuse, that could contribute as cofactors accelerating disease progression. The widespread of HCV-3 in populations with high-risk behaviors could also be an additional reason to prioritize antiviral treatment in order to reduce HCV burden and risk of re-infections. HCV-3 has emerged as the new "difficult to treat" genotype with DAAs as first-generation protease inhibitors (PIs) did not show efficient antiviral activity and also first results from phase III studies with the NS5B polymerase inhibitor Sofosbuvir (SOF) demonstrated that HCV-3 achieved suboptimal SVR rates in patients with advanced liver fibrosis. Indeed, the IFN-free combination of SOF+Rbv achieved more than 90% SVR in naïve and Pegylated (Peg)-IFN+Rbv-experienced patients without cirrhosis receiving a course of SOF+Rbv for 24 weeks in the phase III VALENCE trial, compared to only 27/45 (60%) cirrhotic treatment-experienced patients (30). For these reasons, SOF+Rbv combination for 24 weeks is recommended by current EASL guidelines only in non-cirrhotic patients, while it is considered suboptimal in patients with cirrhosis (8) (Table 1). Another treatment option for HCV-3 patients is a 12-week course of SOF in combination with Peg-IFN and Rbv, which has achieved optimal SVR rates in the BOSON trial also in patients with cirrhosis and previous treatment failure (86% vs >90% in naïve and non-cirrhotic patients, respectively) (31). However, this option is not suitable for patients with decompensated liver disease due to contraindications to Peg-IFN use; moreover, the possibility of administering an IFN-free regimen should be preferred for better treatment tolerability. Combination of SOF with the

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NS5A inhibitor Daclatasvir (DCV) is another effective treatment option in HCV-3 patients: the recommended treatment duration is 12 weeks in non-cirrhotic patients and 24 weeks in compensated and decompensated cirrhosis with addition of Rbv (Table 1). The 24-week plus Rbv schedule has been recommended mainly basing on expert opinions, as in the ALLY 3 trial the 12-week course of SOF+DCV without Rbv reported SVR rates of 58% (11/19) and 69% (9/13) in cirrhotic naïve and experienced patients, respectively (32). The following ALLY-3+ trial demonstrated that the addition of Rbv provided optimal efficacy also with shortened treatment schedules: SOF+DCV+Rbv achieved 100% (14/14) SVR in patients with advanced fibrosis, and 83% (15/18) vs 89% (16/18) SVR in cirrhotic patients with 12 or 16 weeks, respectively (22). In the French compassionate use program in HCV-3 cirrhotic patients, 24 weeks of SOF+DCV with and without Rbv achieved 81% (43/53) and 89% (147/166) SVR rates compared to 100% (5/5) and 81% (47/58) SVR rates in patients treated with 12 weeks of SOF+DCV with and without Rbv, respectively (33).

In conclusion, recent findings from Phase III and real-life studies seem to indicate that in short treatment durations (12-16 weeks) administration of Rbv in patients with advanced fibrosis could be still important to maximize efficacy, whereas in longer treatment course of 24 weeks the role of Rbv could be somehow superseded. However, these data need to be replicated and validated in larger cohorts, so that EASL and AISF recommendations still have to be considered the standard of care for treatment of HCV-3 patients.

Statements

- EASL/AISF recommendations are still the standard of care treatment for HCV-3.

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- Shortened treatment schedules and need for Rbv have to be further evaluated in larger studies.

Treatment of patients with HCV-1a infection

HCV subtype 1a has been considered a "difficult-to-treat category" since the advent of first-generation PIs Telaprevir and Boceprevir, as patients with HCV-1a were at higher risk of virological failure and on-treatment breakthrough in patients with reduced Peg-IFN-sensitivity (partial and null responders). This was the result of the lower genetic barrier of first-generation PIs in HCV subtype 1a, as only one aminoacid substitution was sufficient to develop resistance-associated variants (RAVs) compared to HCV-1b that required instead at least two mutations (34). The reduced efficacy of PIs in HCV-1a is maintained also with second-wave PI Simeprevir (SMV), where the Q80K mutation was associated with lower SVR rates compared to HCV-1b patients, not only with Peg-IFN-based but also with IFN-free combinations. Indeed, in cirrhotic patients treated with SOF+SMV for 12 weeks in the OPTIMIST-2 study, HCV-1a with Q80K achieved 74% SVR compared to 92% in HCV-1a patients without Q80K (25). Due to the high prevalence of the Q80K mutation in the US, the AASLD HCV guidelines do not recommend the use of SMV in HCV-1a patients with cirrhosis and baseline Q80K mutation, who should be treated with other IFN-free regimens (7). HCV-1a with cirrhosis was confirmed also in the real-life setting of the TARGET study as the patient subset with reduced chances of SVR with SOF+SMV (35). Differently from AASLD recommendations, EASL guidelines allow SOF+SMV in HCV-1a cirrhotic patients (without strict need for testing Q80K mutation) with the addition of Rbv when treating for 12-weeks, otherwise treatment should be extended to 24 weeks without Rbv. Anyway, apart from EASL recommendations, baseline NS3 Q80K assessment might be useful to personalize therapy in HCV-1a cirrhotic patients. Non-cirrhotic HCV-1a patients can receive a 12-week course of SOF+SMV

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without Rbv. Administration of SMV is not recommended in patients with decompensated cirrhosis due to increased drug concentrations in impaired liver function resulting in risk for serious adverse events (SAE). The second treatment option for HCV-1a patients is the combination of NS3 PI Paritaprevir boosted with Ritonavir + the NS5A inhibitor Ombitasvir + the non-nucleotide NS5B polymerase inhibitor Dasabuvir, the so-called 3D regimen. In non-cirrhotic HCV-1a patients, the suggested treatment schedule with this combination regimen requires administration of Rbv and a 12-week course. Indeed the phase III study PEARL-IV demonstrated that naïve non-cirrhotic HCV-1a patients receiving 3D combination for 12 weeks benefitted from the addition of Rbv, 97/100 (97%) patients achieving the SVR with Rbv compared to 185/285 (90%) without Rbv, respectively (36). On the contrary, HCV-1b non-cirrhotic patients can be efficiently treated without Rbv, according to the corresponding results of the PEARL-II and III studies (37). When considering patients with cirrhosis, the TURQUOISE II trial compared efficacy of the 3D regimen+Rbv for 12 vs 24 weeks in HCV-1a and 1b patients, showing that the 12-week duration achieved lower SVR rates only in HCV-1a previous null responder to Peg-IFN/Rbv treatment (80% vs >90% in all other HCV-1a patients and HCV-1b irrespectively from treatment experience) (23). These data have led EASL to suggest treatment extension to 24 weeks in HCV-1a patients with cirrhosis, while HCV-1b cirrhotic patients can be efficiently treated for 12 weeks. As for SMV, the 3D regimen is contraindicated in patients with decompensated cirrhosis, due to increased exposure to Paritaprevir in hepatic impairment. This has been also stated by a recent U.S. Food and Drug Administration (FDA) warning concerning cases of severe hepatotoxicity in patients with decompensated cirrhosis (38). The third treatment option for HCV-1a is the combination of SOF with a NS5A inhibitor, either Ledipasvir (LDV) or DCV: due to the higher antiviral activity in HCV-1a subtype compared to NS3 inhibitors, these combinations have been proven to be subtype-

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independent in HCV-1 patients. Indeed, regarding SOF+LDV, the phase III ION program demonstrated that SVR rates exceeded 95% in both HCV-1 subtypes in all treatment durations (8 weeks, 12 weeks and 24 weeks) and independently from fibrosis stage and previous treatment experience, including failures to first-generation PIs (39-41). However, the multi-center HCV-TARGET observational study reported lower rates of SVR in 1a vs 1b cirrhotic patients (42). Combination of SOF with the other NS5A inhibitor DCV showed high efficacy since the phase II trial by Sulkowski and colleagues, with SVR rates ranging from 93% to 100% even in patients with previous treatment failure to PIs (43). Data from the Phase III ALLY-1 trial demonstrated that this regimen provided a good efficacy also in a cohort of patients with advanced cirrhosis treated with SOF+DCV+Rbv, SVR being 76% (26/34) in HCV-1a vs 100% (11/11) in HCV-1b (44). The recently FDA-approved combination regimen with the second generation NS3 inhibitor Grazoprevir (GZR) plus the NS5A inhibitor Elbasvir (EBR) is one of the new treatment options for HCV-1 patients with the possibility of administering a Rbv-free regimen. However, GZR+EBR have demonstrated reduced efficacy in HCV-1a previous Peg-IFN/Rbv non-responders with baseline NS5A RAVs so that treatment extension to 16 weeks is recommended (45). On the contrary, first data with the second-generation NS5A inhibitor Velpatasvir (VEL) in combination with SOF seem to indicate that this regimen could actually be a pangenotypic combination that could provide more than 90% SVR in all patients groups without need for Rbv. Indeed in the ASTRAL-1 study, where cirrhosis represented 20% of patient population, HCV-1a achieved 98% SVR following a 12-week course of SOF+VEL (46). Efficacy remained optimal also in patients with decompensated cirrhosis: the ASTRAL-4 trial compared 12 weeks of SOF+VEL±Rbv with 24 weeks without Rbv in CP B patients, showing no significant differences across all treatment arms, as 83% and 94% patients achieved the SVR in the SOF+VEL 12 week-arm with or without Rbv compared to 86% patients treated with

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SOF+VEL for 24 weeks (47). To date, EASL recommendations still have to be considered the standard of care for treatment of HCV-1a patients (Table 2).

Statements

- EASL/AISF Recommendations are still the standard of care treatment for HCV-1a.

- Some regimens, especially in cirrhotic patients, work better by increasing treatment duration and/or adding Rbv.

- Search for baseline NS3 Q80K might be useful to personalize therapy in HCV-1a cirrhotic patients candidate to start treatment with SOF+SMV, in addition to what already specifically recommended by the Simeprevir drug label.

- Search for baseline NS5A RAVs might be useful to personalize therapy in some selected cases, however it should not be routinely performed, unless if specifically recommended by drug label.

HIV/HCV co-infected patients

The increased availability of antiretroviral therapy against HIV allows HIV-positive patients to live longer, but in this way those who are co-infected with HCV have time to develop the long-term complications associated with HCV infection. In HIV/HCV co-infected patients liver fibrosis progression and the risk of hepatic decompensation are significantly higher than in HCV mono-infected patients (48,49). Moreover HCV itself, through activation of tumor necrosis factor alpha, can participate in immune mediated vascular inflammation, causing activation, adhesion and infiltration of inflammatory cells into the vessels (50). Finally, HCV co-infection in HIV-positive patients increases the risk of death for both all-causes and for liver-related death (51).

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On the other hand, the availability of IFN-free DAAs has dramatically increased the effectiveness of HCV treatment in patients with HIV co-infection and nowadays HIV/HCV co-infected persons should no longer be considered as "difficult to treat patients" as they can be treated as persons without HIV infection. As a matter of fact, virological results using DAAs are the same as mono-infected patients, apart from a greater risk of drug to drug interactions (DDIs) compared to the latter (52-54).

Thus, some patients may need to modify, at least temporarily, the HIV treatment and/or HCV treatment needs to be selected on the basis of previous antiviral treatment history, resistance profiles and drug tolerance, in order to optimize co-administration of both antiviral regimens. Nevertheless, in patients with history of multiple HIV treatment failures receiving a successful antiviral treatment, the usage of DCV+SOF combination could be considered in order not to harm therapeutic control of HIV disease. If DDIs are carefully considered and avoided, all co-infected patients can be safely and effectively treated and the benefit of successful treatment of HCV infection in HIV-infected patients is highly likely to actually go beyond the avoidance of untreated HCV progression, as antiretroviral therapy has repeatedly been found to perform worse in patients with HIV/HCV as compared to those with HIV mono-infection (55).

Statements

- HIV/HCV co-infected patients have a greater inflammation/immune activation condition compared to mono-infected patients.

- HIV/HCV co-infected patients have a greater benefit from HCV treatment compared to mono-infected.

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- Only clinicians with expertise in the management of both HIV and HCV disease are entitled to treat such patients.

- DCV+SOF combination may allow to maintain successful anti HIV therapy when a switch of antiretrovirals may harm HIV disease control.

HBV/HCV co-infected patients

Hepatitis B virus (HBV) and HCV are the most common etiologic factors of chronic liver disease and a major cause of anticipated liver-related mortality worldwide (1,4,5,7,8). Special populations may have concurrent infection with both viruses, as often seen in areas with a high prevalence of HBV infection. Patients with HBV and HCV co-infection are at a higher risk of developing liver cirrhosis and HCC and may need either or both of the anti-HBV and anti-HCV treatments, depending on their viral status, by using therapeutic regimens for HBV or HCV mono-infection (7,8). In the past years, HBV reactivation occurring in HBV/HCV-coinfected patients treated with IFN-based therapy has been reported probably as a consequence of an unbalanced HBV replication caused by treatment-related suppression of HCV, although a direct immunomodulatory effect of IFN might also be advocated for either on- or off-treatment HBV reactivation (56,57). Mitigating these concerns about the use of IFN in HBV/HCV-co-infected patients was the ability of IFN for suppressing HBV replication, resulting in one third of patients with long-term response (8). In contrast, DAAs are not effective for HBV replication, and IFN-free therapy may release HBV from HCV suppressive effects, resulting in HBV reactivation both on- or off-DAAs therapy in HBV/HCV co-infected patients with inactive HBV infection (58,59).

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Statements

- Patients with HBV and HCV co-infection are at a higher risk of liver disease progression.

- In HCV/HBV co-infected patients with detectable serum HBV DNA (> 12 IU/mL) and advanced liver disease the simultaneous administration of anti-HBV nucleos(t)ide analogs treatment and DAAs is recommended.

- In HCV/HBV co-infected patients with inactive HBV infection and without advanced liver disease undergoing DAAs treatment close monitoring of HBV DNA during the anti-HCV DAAs therapy should be considered, in order to start anti-HBV therapy with nucleoside analogs promptly in case of recurrence of florid HBV replication.

Extra-hepatic manifestations

HCV infection is associated with several extra-hepatic manifestations (EHMs) with injury of other than liver organs leading to an increased rate of morbidity and all-cause mortality independently from the degree of liver damage (2,3). The most frequent and investigated EHMs are represented by mixed cryoglobulinemia, resulting in a syndrome characterized by immune complexes deposition within small vessels which may be responsible for a systemic leukoclastic vasculitis mainly involving skin, kidneys, joints, nervous system that ultimately may switch over to NHL. Evidence has also cumulated supporting an association between HCV infection and an increased risk of type 2 diabetes, cerebrovascular and cardiovascular events, chronic renal failure. Recently it has been shown that HCV infection may lead to a substantial reduction in quality of life, with a key role played by depression, cognitive disorders and asthenia (60). The correct diagnosis of HCV-related EHMs is clinically important to ensure early detection of the infection and prevent evolution towards LPD and NHL, starting the best treatment that in the majority of subjects should

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be antiviral therapy with DAAs, despite no significant liver damage (61-64). It should be emphasized that antiviral therapy for HCV was clearly shown to be effective against a wide spectrum of EHMs. However, the fact that not all patients with EHMs having a severe injury to extrahepatic sites clinically benefitted from an SVR warns against the risks of deferring antiviral therapy in asymptomatic patients with HCV-related EHMs. Indeed, it is expected that the multi-step process leading to LPD as well as some of extra-hepatic damage evolution implies a progressive independence from the causative agent with residual symptoms and/or laboratory signs after viral eradication.

Statements

- In patients with cryoglobulins, access threshold for DAAs must not be determined by the liver fibrosis stage but by the evidence of extrahepatic involvement and/or damage.

- Antiviral treatment regimens in such patients have the same schedules and yield similar efficacy compared to patients without cryoglobulins. However among patients with impairment of renal function side effects are higher.

- Renal function is discriminating for the use of SOF-based regimens.

- Not all patients with a severe injury to extrahepatic sites caused by cryoglobulins may fully recover after viral eradication.

Decompensated cirrhosis

The main endpoints in treating patients with decompensated liver disease are to cure HCV infection, to stabilize or improve liver function, reversing decompensation sufficiently to defer LT or

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even to delist patients, or preventing graft re-infection. In these patients the use of new DAAs has been a huge achievement although many issues are still unclear: the optimal treatment duration, if there is a point of no return where viral eradication has no impact on further disease outcome, the need of Rbv and its safety concerns, the DDI, the role of renal impairment, usually present in such patients, and the pharmacokinetics of DAAs that could be impaired in patients with most advanced liver disease.

One randomized controlled study (SOLAR-1) reported the efficacy and safety of SOF+LDV+Rbv in 108 CP B (n=59) or C (n=49) patients (65% treatment-experienced) HCV genotype 1 or 4 treated for 12 (n=53) or 24 weeks (n=55) (65). The overall SVR rate was 87% and 89% in patients treated for 12 or 24 weeks, respectively, and an improvement in MELD score by 1–6 points was reported in 77 (71%) patients. Twenty-eight (26%) patients experienced SAEs but only three discontinued treatment due to these events. Manns et al. reported in 160 treatment-naïve or -experienced (78%) patients with decompensated cirrhosis (CP B:78; CP C:82; HCV-1a: 47%; HCV1b: 42%) who were either awaiting or had received LT (SOLAR-2) the data on safety and efficacy of 12 (n=78) vs 24 (n=82) weeks of SOF+LDV+Rbv. The overall SVR rate was 85% and 88% in patients treated for 12 or 24 weeks, respectively. SVR was associated with improved liver function: 35% of CP B reverted to CP A, while 48% of CP C reverted to CP B and 5% to CP A; 28% of patients experienced SAEs, although only five cases were deemed related to the study drugs (66). Based on the results of the SOLAR 1 and 2 studies FDA has approved 12 weeks SOF+LDV+Rbv for use in genotype 1 CHC patients with advanced liver disease, including those who have undergone liver transplantation. Foster and colleagues through the English expanded access program treated 409 decompensated cirrhotics patients (CP B:72%, CP C:10%) either treatment-naive or -experienced (60%) infected with HCV (HCV-1:49%, HCV-3:42%). Among HCV-1patients: 74% received 12 weeks of SOF/LDV with

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Rbv, 17% were treated with 12 weeks of SOF/DCV with Rbv, and 9% received one of these combinations without Rbv, whereas among HCV-3 patients the corresponding figures were 33%, 61%, and 6%. SVR rates in genotype 1 were 91% for SOF/LDV with Rbv, 85% for SOF/LDV alone, and 88% for SOF/DCV with Rbv, falling to 50% for SOF/DCV alone, whereas among the genotype 3 patients the SVR rates were 65%, 40%, 71%, and 60%, respectively (67). In the open-label ALLY-1 study, 60 treatment naïve (40%) or -experienced patients of any genotype (HCV-1:75%) with advanced cirrhosis (CP B:53%, CP C:27%) received 12 weeks of treatment with DCV+SOF+Rbv. The overall SVR rate was 83%; 94% and 56% in CP B and C, respectively (44). Data from real-life cohorts in decompensated cirrhotics were reported by the multi-center HCV-TARGET observational study. 253 patients (75% HCV-1, 59% prior non-responders) with cirrhosis and a MELD score $\geq$10 who had not undergone LT were treated with SOF-based treatment (SOF+Rbv:102; SOF+SMV:117; SOF+SMV+Rbv:34). Considering only genotype 1 patients, the SVR rates were: 43% for SOF+Rbv, 78% for SOF+SMV and 60% for SOF+SMV+Rbv. HCV-3 patients had the lowest SVR rate, with just 39% being cured (68). The safety and efficacy of SMV+SOF in a real-life cohort of patients with decompensated cirrhosis have been evaluated in an U.S. national study of 156 patients (CP B:49 and CP C:6) treated for 12 weeks with SMV/SOF with (35%) and without (65%) Rbv. Patients with CP B or C developed further hepatic decompensation more frequently and achieved lower SVR rates compared to CP A patients (20% vs 3%; p<0.01 and 73% vs 91%, p<0.01, respectively) (69).

With regard to new DAAs combinations, in the C-SALT study 30 CP B patients (100% HCV-1; mean MELD score 10; 63% treatment-naïve) were treated with a 12-week course of GZR/EBR combination without Rbv. Overall, virological response four weeks after the end of therapy (EOT) was achieved in 90% of patients; two patients relapsed and one developed spontaneous bacterial peritonitis and died because of hepatic failure after EOT (70).

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A recent randomized controlled trial compared 12 weeks of SOF+VEL±Rbv with 24 weeks of SOF+VEL without Rbv in CP B patients. SVR rates were 83% and 86% for patients treated with SOF+VEL for 12 or 24 weeks, respectively, rising to 94% for those who added Rbv. Looking just at HCV-1, the SVR rates were 88%, 92%, and 96%, respectively. Response rates were lower for genotype 3, being only 50% using SOF+VEL alone for 12 or 24 weeks, and 85% with Rbv. At 12 weeks post-treatment, in 47% of patients CP score improved from baseline, in 42% remained stable, and in 11% worsened. Among patients with lower baseline MELD scores (<15), 51% had an improved score, 22% saw no change, and 27% worsened. However, among those with the most severe liver disease, 81% had an improved MELD score, 11% had no change, and 7% worsened. Treatment was generally safe and well-tolerated and about 18% experienced SAEs occurring with similar frequency across arms (47) (Table 3).

The NS34A protease inhibitors SMV, Asunaprevir and Paritaprevir are primarily metabolized by the liver and might, therefore, accumulate in patients with advanced liver failure. Consequently, SMV and the 3D drug combination are not recommended for use in patients with severe hepatic impairment. By contrast, NS5A inhibitors and SOF need no dose adjustment in these patients, while in patients with impaired renal function SOF is not recommended in case of a glomerular filtration rate below 30 ml/minute.

However, the optimal treatment for patients with very advanced liver disease remains unclear. While curing HCV remains a primary goal, effective treatment could potentially reduce a patient's MELD and CP scores lowering their priority on the waiting list, but not enough to prevent need for transplantation in all cases.

The treatment schedules for waitlisted patients do not differ from the schedules defined for advanced and/or decompensated liver disease.

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Among patients on the waitlist for HCC, 61 HCV patients with cirrhosis with CP ≤7 (75% CP A, 100% MELD score <15, 73% HCV-1) received up to 48 weeks of SOF+Rbv before LT (71). 43 of 46 (90%) patients undergoing LT had undetectable HCV RNA at the time of LT and in 30 out of 43 (70%) viremia remained undetectable 12 weeks after LT, 10 (23%) had recurrent infection, and three (7%) died. At the time of transplantation, 92% had a negative viral load, with 69% having an SVR. The only independent predictor of post-LT SVR was the duration of an undetectable viral load prior to transplantation. Only one patient whose HCV RNA was negative for 28 days before transplantation had HCV recurrence. However, most patients on the waiting list have advanced disease, and the option of SOF+Rbv has been shown to be suboptimal.

Statements

- SOF, LDV, DCV can be used in patients with cirrhosis with no need of dose adjustment, whatever the liver impairment.

- Use of SMV is not recommended in decompensated cirrhosis.

- The 3D regimen (Paritaprevir/r, Ombitasvir Dasabuvir) and the 2D regimen (Paritaprevir/r, Ombitasvir) cannot be used in CP C patients and should not be used in CP B patients.

- Use of SOF in patients with eGFR <30 mL/minute is against the label prescription but current experiences suggest that accumulation of SOF and metabolites does not cause specific adverse events.

- DAA combinations achieving a SVR in 12 weeks should be preferred.

- In 20-40% of decompensated patients, antiviral treatment can result in a clinical improvement with reduction of CP and MELD scores. However, this improvement may not

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be sufficient to achieve delisting and, on the other hand, treatment-related MELD score improvement may hamper access to LT (Purgatory Effect).

- Pre-LT DAA treatment is not recommended in patients with high MELD scores (> 25) because of limited probability of improvement, and rapid access to LT. In these patients the option of post-LT treatment with DAAs should be preferable.

- In patients listed for HCC and cirrhosis two conditions can be identified: "low risk" condition, i.e. complete response to HCC bridge therapy, compensated liver disease, expected waitlist time > 3 months according with local donor pool and epidemiology, that can undergo a DAAs treatment aiming for HCV RNA negativity at LT. "High risk" condition, i.e. untreatable HCC or incomplete response to bridge therapy, decompensated liver disease, expected waitlist time < 3 months according with local donor pool and epidemiology, should be prioritized for LT and treated with DAAs in the post-LT period.

Liver transplant recipients

If antiviral treatment is not possible before transplantation, it is recommended after LT in all patients who experience recurrence. However, at this time the possible interactions between DAAs and immunosuppressive drugs should be considered. Indeed, SMV can interact with cyclosporine and Paritaprevir with cyclosporine and tacrolimus (72).

The recurrence of HCV after LT is universal in patients HCV-positive at the time of transplantation, and graft re-infection progresses more rapidly to cirrhosis. On the other hand, SVR has been shown to have a positive impact on both graft and patient survival. In the ALLY-1 study (44), the SVR rate for a 12-week combination of SOF+DCV+Rbv was 94% among LT recipients (n=53) with

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recurrent HCV infection (91% in HCV-3). The combination of DCV with either SOF or SMV for treatment of HCV-1 had been evaluated in 64 LT reporting 85% of SVR rate (73). In a SOF compassionate-use program for patients with severe recurrent HCV infection following LT, 78 patients were treated (44 with SOF/Rbv, 32 with SOF/Rbv plus Peg-IFN, median MELD score 16, 20 with fibrosing cholestatic hepatitis). Among the 27 patients evaluated at 12 weeks after EOT, 15 (56%) patients had SVR. Overall, 75% of these severely ill patients had improved or stable clinical liver disease, including decreased bilirubinaemia, coagulopathy and MELD score (74).

Data available from real clinical practice in 128 patients treated post-LT (25 with F3/4 fibrosis stage) with a 12-week course of SOF+SMV with or without Rbv reported 90% SVR, with lower rates in HCV-1a patients compared to HCV-1b. Very good tolerance and few side effects were reported, with only a minimum adjustment of immunosuppressive treatment, though there was one death related to possible pulmonary toxicity. The addition of Rbv had no impact on the SVR, though the degree of fibrosis did play a role, with reduced SVR in patients with F4 (75). The CORAL-1 study included 34 patients with no or mild fibrosis after post-LT recurrence treated with the 3D regimen plus Rbv for 12 and 24 week (76). An SVR of 97% was obtained in those treated for 12 and 24 weeks, although again an advanced degree of fibrosis reduced the success rate. The most common AEs were fatigue, headache and cough, but no episode of graft rejection was observed during the study.

In a prospective, multicentre, open-label pilot study, 40 patients with recurrent HCV infection of any genotype (HCV-1:85%) and compensated liver disease (bridging fibrosis/cirrhosis:63%) received 24 weeks of SOF+Rbv. SVR was achieved in 28 of 40 patients (70%) and viral relapse accounted for all cases of SVR failure. The most common adverse events were fatigue (30%),

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diarrhoea (28%) and headache (25%). No deaths, graft losses or episodes of rejection occurred and

no interactions with any concomitant immunosuppressive agents were reported (77).

These preliminary results are extremely encouraging and will revolutionize liver transplantation for

HCV-associated disease. Graft and overall survival will be substantially improved. However, most of

these data were derived from patients who did not have cirrhosis. A short series of post-LT severe

recurrent HCV infection treated with an association of SOF+DCV+Rbv demonstrated high efficacy in

term of SVR but high incidence of severe adverse events and death. These data strongly suggested

that antiviral therapy must be initiated before decompensation (78).

Statements

- Prevention of post-LT recurrence based on pre-LT DAA treatment requires a minimal period

    of virological suppression of 28 days.

- Bridging pre/post-transplant therapy could be considered in patients who are still viremic or

    who did not achieve viral clearance for a minimum of 28 days. However, very limited data

    are available concerning DAA pharmacokinetics early after the surgical procedure and

    special attention is required for management of DDI in the early post-operatory period.

    Moreover, post-transplant renal failure needs to be taken into account.

- HCV treatment in LT recipients should not be deferred until severe fibrosis has developed.

    Due to the risk of DDI, particular attention should be paid both during DAAs administration

    and also after the end EOT for the risk sudden drop of immunosuppressant blood levels

    which bears a high risk of rejection.

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Management of patients with treatment failure to IFN-free combinations

Although the development of potent DAAs has represented a revolution in the field of HCV treatment, leading to a substantial increase in efficacy across all patients subsets, treatment failure to new IFN-free combination, even if less frequent than in the past, still represents a major concern. Indeed re-treatment options may not be always available and often patients failing DAAs are also the most-in-need due to decompensated liver disease or other concurrent clinical conditions, so that the lack of efficient re-treatment should be urgently addressed. Treatment failure is a complex condition that can result from combination of some baseline negative patient features (like advanced liver fibrosis) with a suboptimal treatment course. Indeed some IFN-free combinations can be still weak according to genotype and treatment duration (for example administration of 2 DAAs with low genetic barrier, SOF+Rbv combination in HCV-1 patients). As a consequence, the choice of antiviral treatment type and schedule is of paramount importance to optimize chances of SVR in the first treatment course, while the analysis of these same factors after treatment failure is also important to understand potential reasons for not achieving the SVR.

Role of baseline RAVs in treatment failure to DAAs

Due to the lack of proof-reading activity of the HCV RNA-polymerase and the high viral replication rate, a single HCV-infected individual harbors a viral population composed by multiple and different quasispecies; in this setting of extreme genetic variability, viral strains resistant to DAAs naturally occur and preexist drug exposure, being detected with different prevalence according to the sequencing technique used (45). Indeed, while traditional population-based (Sanger) sequencing, mainly used in clinical routine, is able to detect quasi-species representing on average

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at least the 20% of a viral population, deep sequencing (such as Illumina or 454-pyrosequencing), commonly used in research field, provides enhanced sensitivity in RAVs detection, until 1% of a viral population.

The potential role of baseline RAVs in determining treatment failure has been widely discussed: a subanalysis of the SOF+LDV phase II and III studies showed that baseline presence of NS5A RAVs in HCV-1 naïve cirrhotic patients showed a trend on affecting SVR rates when receiving 12 or 24-week course of SOF+LDV in absence of Rbv (12-week arm:88% <u>vs</u> 95%; 24-week arm:85% <u>vs</u> 100% with or without NS5A RAVs, respectively) (79). This difference was almost abolished if patients were treated also with Rbv (with baseline NS5A RAVs, 12-week arm+Rbv: 94% and 24-week arm+Rbv: 100%). Baseline role of RAVs in treatment failure has not been confirmed in most analyses of clinical trials across many different DAAs, despite high RAVs prevalence in some patient populations. Indeed in a pooled analysis of SOF+DCV phase II and III studies, baseline RAVs, which were detected in almost 12% of patients, did not affect treatment outcome in non-cirrhotic patients receiving SOF+DCV±Rbv for 12 weeks (80). The only exception is represented by SOF+SMV, where instead the Q80K mutation has been associated with significant SVR rates reduction in HCV-1a (25), so that baseline assessment of Q80K is recommended by AASLD guidelines in order to avoid SMV administration in Q80K carriers with cirrhosis. Another regimen influenced by baseline RAVs is the shortcoming GZR+EBR combination, where SVR to GZR+EBR for 12 weeks drops to 67% and 29% respectively in HCV-1b and 1a patients previous non-responder to Peg-IFN+Rbv carrying RAVs to EBR. Of note, prevalence of these RAVs ranges from 10% to almost 20% (45). However, baseline RAVs seem to be overcome by prolonging treatment, so that a 16-week course is recommended by the recently approved FDA label for these drugs.

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Role of RAVs after treatment failure to DAAs

Failure to DAA-based regimens frequently results in RAVs selection, particularly in case on non-response or viral breakthrough, as drug pressure modify viral population, that is progressively enriched in resistant strains with respect to wild-type ones (81). At the time of virological failure, particularly after a NS5A-containing regimen, patients carry RAVs to almost one DAA they have been exposed to (82). In patients who failed after receiving 12 or more weeks of treatment with 3D-regimen with or without Rbv, RAVs were selected in all 3 targets, while most patients who relapsed after 8 weeks of treatment did so without any detectable RAVs (83) The clinical relevance of different RAVs is mainly driven by their persistence, as some mutated viral strains may not display good replicative fitness, so that they can be progressively replaced by the wild-type virus as the drug selective pressure ends. On the contrary, other RAVs show the same fitness as wild-type virus, so persisting detectable long-term. This is of relevant clinical importance, because some specific RAVs have cross-resistance in the same drug family, so that re-treatment in these cases requires changing DAA class and different therapeutic approaches, such as treatment extension or addition of Rbv. As a consequence, resistance testing in a patient failing a DAA-based regimen is mandatory in order to optimize the re-treatment strategy, and should be performed at virological failure in all three genes (NS3, NS5A and NS5B) in order to better guide retreatment decisions.

Due to the high conservation of RNA polymerase catalytic site, aminoacid substitutions in this region result in viral strains with extremely low replicative fitness, so that the most commonly described RAV to SOF, the S282T, is rapidly no longer detectable (84). As a consequence, retreatment of SOF-failed patients with SOF-containing regimens yields optimal efficacy, resulting in same SVR as naïve patients (85,86). NS3-associated RAVs selected with the new NS3 inhibitors such as SMV or Paritaprevir, or GZR, also, have frequently a low-intermediate replicative fitness,

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and long-term follow-up studies demonstrated that the majority of NS3 RAVs selected by these NS3 inhibitors tend to be progressively lost and replaced by wild type virus, so that within one year in the majority of patients the entire viral population has nearly reverted to wild type virus (87-89). However, it has been shown that some RAVs absent with the population sequencing can be still detected by deep sequencing (90). For these reasons, while population sequencing can be used for resistance analysis at virological failure, deep sequencing, if available, could better guide retreatment options if the second treatment is deferred. NS3 RAVs can be overcome if retreating patients by shifting to another drug class like NS5A inhibitors, and this has been clearly demonstrated by high SVR rates achieved in patients with a previous treatment failure to PIs in the Phase II study with SOF+DCV by Sulkowski (43) and the ION-2 trial with SOF+LDV (40). RAVs to NS5A inhibitors are instead of major clinical relevance in case of treatment failure, as these variants show optimal replicative fitness and are able to persist long-term (91,92) conferring also cross-resistance to other NS5A inhibitors. However, the effect of NS5A RAVs after failure to a first treatment course strongly depends on the type of mutation and also of the HCV genotype (93).

For instances, a recent study evaluating efficacy of a 24-week course with SOF+LDV in patients previously failing 8 or 12-weeks with the same SOF+LDV combination showed that SVR decreased in parallel with number of detectable baseline NS5A RAVs. Indeed SVR rates dropped from 100% in absence of baseline NS5A RAVs to 50% in case of 2 or more detectable RAVs, reaching 33% in presence of the Y93H NS5A substitution, which confers high level of resistance to LDV. Of note, the likelihood of developing NS5A RAVs increased in patients exposed to SOF+LDV for longer treatment courses (94). As a consequence, re-treatment strategy in patients failing NS5A-based regimens should not be based on a NS5A-containing combination, unless the resistance testing showed absence of NS5A RAVs or presence of a specific NS5A RAV that does not necessarily

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confers cross-resistance to all the class; on the contrary, these patients could be treated by shifting drug class to a NS3-containing regimen, like SOF+SMV (95).

The most difficult therapeutic approach is the management of patients harboring RAVs to multiple DAA classes, for example NS5A plus NS3: these patients currently have no chances of re-treatment with commercially available IFN-free combinations and could be managed only with by multiple DAA combinations targeting nearly all replication steps, such as a NS5B nucleotide polymerase inhibitor±NS5B non-nucleotide+NS5A+NS3 inhibitor. This approach is currently under evaluation in some clinical trials, such as the IMPACT trial with SOF+SMV+DCV in HCV-1 and 4 patients with decompensated liver disease (96) or the QUARTZ-I trial with the 3D combination regimen+ SOF+Rbv (97) in DAA-experienced patients, reporting preliminary optimal SVR rates. These data have to be confirmed in larger studies, however "unconventional" approaches out of drug labels/market reimbursement need cooperation from drug companies and refining of national reimbursement policies to be translated in clinical practice. In the meantime, drug research is moving forward to develop next generation DAAs with improved resistance profile, first in line NS5A inhibitor VEL and NS3 protease inhibitor ABT-493+NS5A inhibitor ABT 430, that could provide efficient retreatment options in the near future.

Statements

- Baseline resistance testing for RAVs before first course with DAAs has limited clinical utility, unless if recommended by specific drug labels.

- In case of baseline presence of NS5A RAVs or Q80K, the search of other baseline NS3 and NS5a RAVs might be useful to personalize therapy, and should encourage the use of at least

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2 active DAAs without resistance and/or longer treatment duration and/or the addition of Rbv.

- Resistance testing after treatment failure in all 3 genes (NS3, NS5A, NS5B [for the two different classes of nucleoside and non- nucleoside inhibitors] independently of the failure regimen) is strongly recommended in order to optimize retreatment strategy*.

- HCV sequencing can be based on Sanger population method and should also confirm the previous genotype and subtype assignment.

- According to resistance results, current re-treatment strategies for patients failing a first course with DAAs should include at least 2 active drug classes, with a preferential use of one drug with high genetic barrier to resistance, and with extended treatment durations and addition of Rbv, otherwise waiting for better future options.

- If a deferred treatment has been considered, and in case of presence of RAVs at failure, in order to assist the therapeutic choice when starting a re-treatment, HCV sequencing should be repeated (only in the gene with previous RAVs) and should be better based on deep sequencing.

* NOTE: It would be desirable to preserve a sample before starting treatment with DAA, because in case of failure and presence of RAVs, the study of the baseline sample may help to distinguish if the resistance occurred during failure or it was already present as natural resistance before treatment. This information may help to set to the best the next regimen.

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Conclusion

The availability of all oral IFN-free treatment regimens has changed the approach to treating CHC patients. These treatments are highly effective, well-tolerated and enable clinicians to treat all infected patients. Achieving the SVR reduces liver disease progression and solves the HCV-related extra hepatic manifestations, reducing both liver-related and overall mortality. Several national and international guidelines have been published until today to help clinicians in the management of CHC patients. However, these recommendations may not be applied worldwide due to the treatment prioritization based on high costs of therapies. This position paper sought to solve some of the gaps of the guidelines and to answer the few unmet needs on treatment optimization.

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Table 1. Interferon-free regimens recommendations for genotype 3 patients with chronic hepatitis C with or without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on Peg-IFN and Rbv (PR) (8).

	SOF+Rbv	SOF+DCV
No cirrhosis	24 wk	12 wk
Compensated cirrhosis (CP A)	NO	24 wk+Rbv
Decompensated cirrhosis (CP B and C)	NO	24 wk+Rbv

Table 2. Interferon-free regimens recommendations for genotype 1a patients with chronic hepatitis C with or without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on Peg-IFN and Rbv (PR) (8).

	3D	SOF+LDV	SOF+DCV	SOF+SMV
No cirrhosis	12 wk+Rbv	8/12 wk	12 wk	12 wk
Compensated cirrhosis (CP A)	24 week+Rbv	12 wk+Rbv 24 wk w/out Rbv	12 wk+Rbv 24 wk w/out Rbv	12 wk+Rbv* 24 wk w/out Rbv*
Decompensated cirrhosis (CP B and C)	NO	12 wk+Rbv 24 wk w/out Rbv	12 wk+Rbv 24 wk w/out Rbv	NO

* Search for baseline NS3 Q80K might be useful to personalize therapy in HCV-1a cirrhotic patients, in addition to what already specifically recommended by the Simeprevir drug label.

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FROM CURRENT STATUS TO OPTIMIZATION OF HCV TREATMENT: RECOMMENDATIONS FROM AN EXPERT PANEL

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Zignego AL: speaker bureau for BMS, Gilead Sciences, MSD, Janssen

Table 3. Interferon-free regimens in HCV-related decompensated cirrhotic patients.

	SOLAR 1[65]	SOLAR 2[66]	UK expanded access program[67]	ALLY-1[44]	TARGET[68]	Saxena et al[69]	Curry et al[47]
Nr of patients	108	160	409	60	253	156	267
CP score B/C	55%/45%	49%/51%	72%/10%	53%/27%	53%/27%	31%/4%	90%/4%
DAA regimen	SOF+LDV+R	SOF+LDV+R	SOF+LDV±R SOF+DCV±R	SOF+DCV+R	SOF+R:40% SOF+SMV:46% SOF+SMV+R:14%	SOF+SMV+R:35% SOF+SMV:65%	SOF+VEL±R:35% SOF+VEL:65%
Treatment duration	12 wk:53 pts 24 wk:55 pts	12 wk:78 pts 24 wk:82 pts	12 wk	12 wk	12 wk	12 wk	12 wk SOF+VEL±R 24 wk SOF+VEL
SVR	12 wk:87% 24 wk:89%	12 wk:85% 24 wk:88%	HCV-1 SOF+LDV±R:85-91% SOF+DCV±R:50-88%	CP B:94% CP C: 56%	In HCV-1 SOF+R:43% SOF+SMV:78% SOF+SMV+R:60%	CP A:91% CP B/C:71%	12 wk SOF+VEL:83% 12 wk SOF+VEL+R:94% 24 wk SOF+VEL:86%

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