ROMANIAN SGH* CORNER

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# Position Paper on Treatment of Hepatitis C in Romania, 2017. Part One

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## ABSTRACT

**Background & Aims**: Hepatitis C Virus (HCV) infection is a common condition with endemic prevalence in some areas of the world. In Romania, the mean prevalence is about 3%. New treatments became available on the market in recent years and new drugs are in the pipeline. A re-evaluation of HCV therapy was considered mandatory. The Romanian Society of Gastroenterology and Hepatology undertook this task for the practitioners of this country.

**Methodology**: A group of recognized experts was created who screened the available literature and the major available guidelines. A list of items requiring attention has been created. These items were discussed and rated. Decisions were taken by consensus.

**Recommendations**: We present here the first of the two parts of our Society's recommendations for chronic HCV infection treatment. An agreement was reached regarding the diagnostic tools, the assessment of severity and the up-dated therapy schedules.

**Conclusions**: This Position Paper represents a guide for the assessment and the therapy of HCV infection. The recommendations are in concordance with other guidelines but are applied to the real-life conditions in this country.

**Key words:** Hepatitis C Virus – Guideline – Diagnosis – Treatment – Direct Antiviral Agents – National Strategy – Viral hepatitis C.

**Abbreviations**: DAAs: Direct-acting antivirals; DDIs: Drug-drug interactions; ESLD: End-stage liver disease; ESRD: End-stage renal disease; eGFR: Estimated glomerular filtration rate; EASL: European Association for the Study of the Liver; EMA: European Medicines Agency; FDA: US Food and Drug Administration; FDC: Fixed-dose combination; GT: Genotype; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; LT: Liver transplantation; LLD: Lower limit of detection; MELD score: Mayo-Clinic End-Stage Liver Disease score; ANMDM: National Agency of Medicines and Medical Devices; PPIs: Proton pump inhibitors; PWID: People who inject drugs; RCT: Randomized controlled trial; RDT: Rapid diagnostic test; RAS: Resistance-associated substitution; SRGH: Romanian Society of Gastroenterology and Hepatology; SAE: serious adverse events; SPC: Summary of Product Characteristics; SVR: Sustained virologic response.

## INTRODUCTION

Hepatitis C virus (HCV) infection is a main contributor to chronic liver diseases worldwide, currently affecting 170-200 million individuals (3% of the world's population) [1-5]. Long-term HCV infection translates to a heavy burden of liver-related morbidity and mortality, mainly due to liver complications such as liver cirrhosis, liver failure and hepatocellular carcinoma (HCC), causing about 350,000-500,000 deaths yearly worldwide [6-8]. In addition, many extrahepatic manifestations have been reported to contribute to chronic HCV infection related morbidity and mortality, including type 2 diabetes and insulin resistance, systemic vasculitis, cardiovascular diseases, neurocognitive dysfunction, B cell non-Hodgkin lymphoma and chronic kidney disease [9, 10]. Despite the tremendous morbidity and mortality of chronic HCV infection, about 50% of the affected individuals are unaware of their infection, irrespective of its stage [11].

The most recent seroprevalence data on HCV infection in Romania have shown a rate of anti-HCV positive antibodies of 2.7-5.6% depending on the study population and methodology [12-14]. Based on a highly representative nationwide cross-sectional survey showing an anti-HCV prevalence of 3.23% in the adult Romanian population [15], there was an estimation of 553,017 HCV RNA positive individuals in 2014, equating to a viremic prevalence of 2.72% in our country [16]; however, only an estimated 16% of cases have been diagnosed so far [17].

Genotype 1 (GT-1) is the most prevalent genotype in Romania; it is diagnosed in 99% of all infected patients, with a significant majority (99%) of GT-1b subtype; other genotypes may only be sporadically diagnosed [18]. The majority of HCV infected patients in Romania have acquired the disease through blood or blood products transfusion before 1993 or through exposure to unsafe medical procedures in the early 80's [15]; more recently, injecting drug use and high-risk sexual practices became important routes of HCV transmission and might be anticipated to increase in the coming years. The peak prevalence of HCV infection was observed among persons older than 45 years, with females significantly more affected than males, possibly due to the higher exposure to unsafe medical procedures (illegal abortions) in the communist era [15].

In Romania, HCV infection has been identified as the main cause of chronic hepatitis (64%) and liver cirrhosis (59%) [19] and it is the leading indication for liver transplantation (LT), accounting for 31.5% of all LT procedures performed in our program in 2012 [20]. Most HCV infected patients remain usually asymptomatic or have only mild nonspecific symptoms until the liver disease advances and its complications occur; consequently, diagnosis of HCV infection is usually performed by incidental detection of abnormal laboratory markers (mildly elevated aminotransferases) or of HCV infection (anti-HCV antibodies).

The introduction of oral direct-acting antivirals (DAAs) has revolutionary changed the management of patients with chronic HCV infection. In the current era, sustained virologic response (SVR) is achievable in the vast majority (>90%) of HCV-infected patients, including groups traditionally viewed as „difficult-to-cure", by using highly efficient, short-term and well-tolerated DAA combinations. In addition, the current available therapeutic options have been associated with marked improvement in safety, simplicity of treatment regimen and monitoring, and fewer treatment contraindications [21]. Finally, SVR benefits have been proved to be associated with reduction in the rates of liver complications, HCC, and liver-related mortality; additional benefits include reduced morbidity related to extrahepatic and systemic manifestations of chronic HCV infection such as renal, autoimmune, and metabolic complications [22].

## METHODOLOGY

This Position Paper has been prepared by a panel of experts appointed by the Board of the Romanian Society of Gastroenterology and Hepatology (SRGH) based on their expertise in the diagnosis and treatment of HCV infection. These recommendations are based on written publications in peer-reviewed journals (prospective randomised controlled trials (RCTs) phase III with high power and no major biases; multicentre cohort studies; case-control studies; outcome research studies; systematic review of randomized controlled studies; systematic review of cohort studies; systematic meta-analyses and reviews, consensus recommendation of international and national societies), presentations at national and international meetings and, if evidence was not available, on experts' personal experiences and opinion.

To grade the evidence and recommendations we assumed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [23], also used by the European Association for the Study of the Liver (EASL) in EASL Recommendation on Treatment of Hepatitis C 2016 [24] (Table I). Accordingly, the quality of evidence in this Position Paper has been classified into one of three levels: high [A], moderate [B], or low [C]. Consequently, the GRADE system offers two grades of recommendation: strong [1] or weak [2] (Table I) [23]; thus, the strength of recommendations reflects the quality of evidence from existing data.

**Table I.** Grading used for evidence of quality and recommendations (adapted from the GRADE system)

| **Evidence of quality** | | **Grading** |
|---|---|---|
| High | Further studies are very unlikely to change the confidence in current evidence and to impact the current recommendations | A |
| Moderate | Further studies are likely to change the confidence in current evidence and to impact the current recommendations | B |
| Low | Further studies are very likely to change the confidence in current estimates and to impact the current recommendations | C |
| **Recommendation** | | |
| Strong | The strength of recommendation is high based on the high evidence level of quality, presumed outcome in clinical practice with acceptable cost | 1 |
| Weak | The strength of recommendation is weak based on the low evidence of quality, less certainty of outcome, higher cost or resource consumption | 2 |

The statements comprised in this SRGH Position Paper originate from a working session which took place on December 5, 2016 in Bucharest, and 3 other on-line sessions. Finally, in March 2017, the current recommendations fulfilled all the criteria for the approval of the SRGH Board in order to be published in the Journal of Gastrointestinal and Liver Diseases.

The Position Paper on the management of chronic HCV infection issued by SRGH is aiming to provide up-to-date recommendations and to assist Romanian physicians (gastroenterologists and infectious diseases specialists) to find the best possible therapeutic approach in treating hepatitis C in Romania in 2017. These recommendations are based on the best available evidence and consider only the currently licensed drugs and regimens that have been approved in European Union and our country at the time of publication. They will be updated periodically following approval of new drug regimens by the European Medicines Agency (EMA) and the National Agency of Medicines and Medical Devices (ANMDM). The

electronic version of this Position Paper, as well as periodically up-dated versions will be available at the site of SRGH (*www.srgh.ro*) and at *www.hepatologycourse.ro*. As further research will provide new data, information and tools that will significantly change the current estimates and substantially impact the current recommendations, a new version of this Position Paper will be considered for publication.

The 14 chapters of the Position Paper, listed below, will be published in two consecutive issues of the journal (volume 26 issues 2 and 3, 2017).

1. Screening for chronic hepatitis C
2. Diagnosis of chronic hepatitis C
3. Endpoints and goals of therapy
4. Indications for therapy
5. Contraindications to therapy
6. Pre-therapeutic assessment
7. Approved and available therapeutic regimens
8. Individualized therapeutic recommendations according to genotype and fibrosis stage
9. Special therapeutic groups of chronic HCV infection
10. Therapeutic monitoring and response assessment
11. Dose reduction and treatment discontinuation
12. Support measures/programs aiming to improve access, adherence and efficacy of therapy
13. Follow-up of patients who achieved SVR
14. Re-treatment of patients with treatment failure

## KEY RECOMMENDATIONS

### 1. Screening for chronic hepatitis C

Screening strategies for HCV infection should be based on the local epidemiology and ideally incorporated in a long-term national plan aiming at HCV elimination [A1].

Systematic one-time testing is highly recommended in our country due to the high HCV endemicity in the Romanian population. Screening for HCV infection should be performed in high risk groups consisting of people with exposures, behaviors or conditions associated with increased risk of HCV infections (Table II) [A1]. In persons with ongoing risk factors for exposure to HCV, periodic testing should be recommended (Table II). In addition, in Romania, where the majority of HCV infected individuals belong to a well-defined age group (older than 45 years), birth cohort testing might represent the optimal national screening approach in a long-term strategy aiming at HCV elimination [15, 25].

Screening for HCV infection is based on the detection of anti-HCV antibodies [A1] performed by 3rd generation Enzyme Immunotest Assays (EIAs) in serum or plasma, or rapid diagnostic tests (RDTs) using plasma, serum, fingerstick, whole blood or saliva [26] [A1]. If the anti-HCV test is positive, HCV RNA should be determined by a sensitive molecular method to identify viremic patients [A1].

Until a national screening programme, as part of a National Strategy of HCV Elimination, will be adopted in Romania ensuring the infrastructure and funding, SRGH recommends screening for all patients older than 45 and those at high risk (Table II) [A1]. Systematic consideration for screening should be given to all patients fulfilling these criteria who present at Emergency services, at an Outpatient Clinic or are admitted into the hospital (in these settings the anti-HCV test could be performed without payment by the patients) [A1].

**Table II.** Persons with exposures, behaviors or other conditions associated with an increased risk of HCV infection in whom one-time testing should be performed

| |
|---|
| **Risk exposures** |
| Persons with percutaneous/parenteral exposures during maneuvers in unsafe/unregulated setting |
| Persons on long-term hemodialysis |
| Healthcare and public workers |
| Children born to HCV-infected mothers |
| Recipients of blood or blood products transfusions or organ transplants before 1995 |
| Incarcerated persons current or ever |
| **Risk behaviors** |
| Persons who inject drugs (PWID) current or ever |
| Intranasal illicit drug use |
| Men who have sex with men (MSM) |
| Persons with multiple sexual partners whom HCV status is unknown |
| **Other considerations** |
| HIV infection |
| Unexplained chronic liver disease or elevated aminotransferases |
| Solid organ donors (deceased or living) |

### 2. Diagnosis of chronic hepatitis C

Diagnosis of HCV infection may be performed by screening or by routine evaluation of patients showing clinical signs/symptoms suggestive of chronic liver disease or abnormal laboratory markers (mildly elevated aminotransferase levels), compatible with HCV chronic infection.

Anti-HCV antibodies are the first line diagnostic test [27] [A1]; if positive, HCV RNA by a sensitive molecular method [24, 27] [A1] or, if not available/affordable, HCV core antigen should be determined [A1] to identify patients with chronic infection. HCV core antigen is less sensitive than HCV RNA assay [28] and the SRGH does not recommend its routine use in current practice in Romania [A2]. Anti-HCV positive and HCV RNA negative individuals should be retested for HCV RNA within 3 to 6 months to confirm HCV spontaneous cure [A1]. In immunocompromised patients, HCV RNA testing should represent the initial evaluation [A1], as anti-HCV antibodies are not reliable in this population.

### 3. Goals and endpoints of therapy

The long-term goal of therapy in chronic hepatitis C is to prevent progression to end-stage liver disease (ESLD) and HCC, to decrease the rate of hepatic and extrahepatic complications and to reduce liver-related and all-causes mortality by eradication of HCV infection [A1].

The immediate endpoint of therapy is to eradicate HCV infection by achieving sustained virological response (SVR) defined as undetectable HCV RNA in blood by a sensitive assay

(lower limit of detection or LLD ≤15 IU/ml) at 12 (SVR12) and/or 24 (SVR24) weeks after stopping therapy) [A1]. Both SVR12 and SVR24 have been accepted as endpoints of therapy by regulatory authorities in the United States and Europe, given their concordance higher than 99% [29]. Long-term follow-up studies have shown that achieving SVR represents the definitive cure of HCV infection as it is maintained permanently in more than 99% of cases [30].

In patients with advanced fibrosis and cirrhosis, HCV eradication has been proved to reduce the rate of decompensation and complications, but the impact on the development of HCC is still controversial. Therefore, in these patients, systematic surveillance for HCC should be continued and the SRGH strongly recommends surveillance for HCC in the first 2-5 years after achieving SVR in cirrhotic patients [A1].

## 4. Indications for therapy

SRGH recommends antiviral therapy unrestrictedly in all treatment-naïve and treatment-experienced patients with HCV-related compensated and decompensated liver disease, who consent to be treated and have no contraindications to therapy [A1].

Initiating therapy in earlier stages of liver disease (low-stage fibrosis) is associated with increased efficacy and tolerability and augments the benefits of SVR, while treatment delay may decrease it [31-33][A1].

Treatment must be considered immediately in the following categories of patients due to the potential of severe outcome or the risk of HCV transmission [24, 33] [A1]:

- patients with compensated (F4 METAVIR score) and decompensated cirrhosis (MELD score less than 18-20);
- patients with significant fibrosis (F2 and F3 METAVIR score);
- patients with clinically significant extrahepatic manifestations of HCV infection (e.g. HCV-related mixed cryoglobulinemia with symptomatic vasculitis, HCV immune-mediated nephropathy, B-cell non-Hodgkin lymphoma etc.);
- patients with HCV recurrence after LT;
- patients at risk of rapid progression of liver disease due to concurrent comorbidities (e.g. diabetes mellitus etc.);
- individuals at risk of transmitting HCV infection: people who inject drugs, men who have sex with men, high-risk sexual practices, incarcerated and institutionalized individuals, patients on chronic hemodialysis, women anticipating pregnancy.

Although we agree that some patients are in greater need for immediate treatment (the above mentioned categories), we do not consider that financial and political constraints should be held as primary decision factors and subsequently deny access to therapy (cure) to those who would have the maximum benefit from SVR (eg. patients with earlier stages of liver disease, women with childbearing potential etc.) [A1].

## 5. General contraindications to therapy

There is no absolute contraindication to the DAAs regimens in 2017. Treatment is not recommended in patients with short life expectancy due to hepatic or extrahepatic conditions that cannot be resolved by HCV eradication, LT or other specific curative therapies [B2].

## 6. Pre-therapeutic assessment

Pre-therapeutic assessment of HCV-infected patients includes:

1) virusologic assessment (HCV RNA quantification, HCV genotype determination, HCV resistance testing);

2) assessment of liver disease severity;

3) evaluation for other causes of liver injury. These are important tools for deciding and tailoring antiviral therapy.

### *6.1. Virusologic assessment*

HCV RNA detection and quantification by a sensitive assay with a lower limit of detection (LLD) of ≤ 15 IU/ml is essential to link HCV replication to liver disease [A1], as not all anti-HCV positive patients detected by screening are viremic (only approximately 80%).

Genotyping and GT-1 subtyping (1a or 1b) should be performed routinely before therapy initiation in order to select the appropriate antiviral regimen [A1], taking into account that some of the currently approved DAA regimens are not pan-genotypic or different regimens are recommended in GT 1a or 1b infected patients. Despite the very high prevalence of GT-1b in the Romanian cohort infected through exposure to unsafe medical procedures in the early 80's [19], the SRGH strongly recommends HCV genotyping anticipating changes that might occur in GT distribution in the coming years due to increasing HCV infection through high-risk sexual practices and injecting drug use.

There are no standardized commercially available tests for HCV resistance to approved drugs. Resistance testing relies on inhouse techniques based on populations sequencing (reporting resistance–associated substitutions, RASs, as „present" or „absent") or deep sequencing (only RASs that are present in more than 15% of sequences generated are considered) [B1] [34]. Because access to reliable HCV resistance testing is not universally available and there is no consensus on the techniques or the interpretation of these tests, SRGH does not recommend systematic assessment of HCV resistance prior treatment at this moment [B1] [35]. Even the utility of HCV resistance testing prior re-treatment in non-SVR patients who failed on any DAA regimens is not yet determined [35]. If reliable resistance testing can be performed, SRGH recommends that re-treatment should be guided according to resistance profile and the regimen should be decided by a multidisciplinary expert team including an expert gastroenterologist, virologist and adherence support team [B2] [35, 36].

### *6.2. Assessment of liver disease severity*

Assessment of liver disease severity is recommended prior to therapy, in order to identify patients with advanced fibrosis and cirrhosis, as the choice of the DAA regimen (combination, duration) and the post-treatment prognosis and surveillance depend on the stage of fibrosis [A1].

Liver disease severity assessment can be performed invasively (liver biopsy) [37] or non-invasively (using biological

tests or elastographic methods) [38]. Due to its limitations in the diagnosis of disease severity [39], discomfort and complications, the use of liver biopsy decreased in daily practice in many regions [40]. Nowadays, in chronic hepatitis C, considerable evidence suggests that fibrosis stage can be assessed by non-invasive tests (liver stiffness measurement, blood biomarkers), liver biopsy remaining an indication in case of uncertainty or in cases of known or suspected additional causes of liver injury, e.g. HBV co-infection, metabolic syndrome, alcoholic or autoimmune liver disease) [41] [A1].

Non-invasive modalities for liver fibrosis assessment have been increasingly used in practice in the last 5-10 years. Biological tests (from very simple ones such as APRI or FIB-4 to more complex ones, such as FibroActiTest or Fibromax) are frequently used. Complex tests (FibroActiTest or Fibromax) have high accuracy rates and can be confidently used in daily practice for liver disease severity assessment [42]. The cut-off values for F0 METAVIR are 0.00 to 0.21; for F0-F1 0.22 to 0.28; for F1 METAVIR 0.29 to 0.31; for F1-F2 0.32 to 0.48; for F2 METAVIR 0.49-0.58; for F3 METAVIR 0.59-0.72; F3-F4 METAVIR 0.73-0.74 and for F4 METAVIR 0.75-1.00 (http://www.biopredictive.com/intl/physician/fibrotest-for-hcv/view?set_language=en). Elastographic methods (especially the ultrasound-based ones) can assess liver fibrosis severity with an accuracy of 80 to 95%, increasing with the severity of fibrosis [43, 44]. Transient Elastography (using FibroScan®, Echosens, Paris) is the oldest and best validated method for liver fibrosis assessment [38]. The cut-off values proposed for HCV patients are the following: 7 kPa for F2, 9.5 kPa for F3 and 12 kPa for F4 [44]. Other ultrasound based elastographic methods [such as point share-wave elastography (SWE) (VTQ and Elast PQ) or 2D-SWE] were proposed, with good value for liver fibrosis assessment [45, 46]. Magnetic Resonance Elastography (MRE) has been initiated, especially in the USA, for liver fibrosis evaluation. The combination of liver stiffness measurement and blood biomarkers improves accuracy and limits the need for liver biopsy in uncertain cases [38].

In the last decade, Romanian physicians have started to use extensively the noninvasive methods for liver fibrosis assessment (Fibroscan and Fibromax) and a great deal of expertise has been accumulated. Subsequently, SRGH recommends systematic evaluation of liver fibrosis using either Fibroscan or Fibrotest (Fibromax), depending on local availability and expertise [A1]. Fibroscan is the preferred technique for cirrhosis assessment, due to its ability to stratify the severity and outcome of liver cirrhosis [A1].

Patients should be carefully assessed for the presence and severity of concomitant cardiac, respiratory and renal diseases that might impose limitations on antiviral therapy [A1].

### *6.3. Evaluation for other causes of liver disease*

Other causes of liver disease or factors which can affect the natural history of chronic liver disease or therapeutic regimen selection should be systematically investigated and the possibility of drug-drug interactions (DDIs) and toxicity during antiviral therapy should be assessed (HBV and HIV co-infections, alcoholic or metabolic liver disease, genetic or autoimmune liver disease) [A1]. Patients with other concomitant causes of liver injury should be prioritized for antiviral therapy, especially if corrective measures cannot be implemented, as the progression of their liver disease is faster [B1].

## 7. Approved and available therapeutic regimens

To date only the following HCV drugs/regimens have been registered in Romania: Sofosbuvir (Sovaldi®, Gilead Sciences), Daclatasvir (Daclinza®, Bristol-Myers Squibb), Simeprevir (Olysio®, Janssen Pharmaceuticals), Ribavirin, the fixed dose combination Sofosbuvir/Ledipasvir (Harvoni®, Gilead Sciences.), the combination Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir (3D regimen) (Viekirax-Exviera®, AbbVie Pharmaceuticals), and the fixed dose combination Grazoprevir/Elbasvir (Zepatier®, Merck Sharp & Dohme) (Table III). A comprehensive presentation of their pharmacokinetic profiles and DDIs can be found in the electronic version of this Position Paper, the EASL Recommendations on Treatment of Hepatitis C 2016 [24], the Summary of Product Characteristics (SPC) for each drug, and at www.hep-druginteractions.org. The potential harmful

**Table III.** Approved HCV DAAs in Europe and Romania in 2017

| | Presentation | Posology |
|---|---|---|
| Sofosbuvir | Tablets containing 400 mg of Sofosbuvir | 1 tablet once daily (in the morning) |
| Sofosbuvir/Ledipasvir | Tablets containing 400 mg of Sofosbuvir and 90 mg of Ledipasvir | 1 tablet once daily (in the morning) |
| Sofosbuvir/Velpatasvir | Tablets containing 400 mg of Sofosbuvir and 100 mg of Velpatasvir | 1 tablet once daily (in the morning) |
| Ritonavir/Paritaprevir/Ombitasvir | Tablets containing50 mg of ritonavir, 75 mg of Paritaprevir and 12.5 mg of Ombitasvir | 2 tablets once daily (in the morning) |
| Dasabuvir | Tablets containing 250 mg of Dasabuvir | 1 tablet twice daily (in the morning and evening) |
| Grazoprevir/Elbasvir | Tablets containing 100 mg of Grazoprevir and 50 mg of Elbasvir | 1 tablet once daily (in the morning) |
| Daclatasvir | Tablets containing 60 mg of Daclatasvir | 1 tablet once daily (in the morning) |
| Simeprevir | Capsules containing 150 mg of Simeprevir | 1 capsule once daily (in the morning) |
| Ribavirin | Capsules containing 200 or 500 mg of Ribavirin | 2 capsules in the morning and 3 capsules in the evening if body weight<75kg, 3 capsules in the morning and 3 capsules in the evening if body weight≥75kg |

DDIs should be systematically checked before the initiation of any DAAs regimen at www.hep-druginteractions.org, as new DDIs maybe reported.

## 8. Individualized therapeutic recommendations according to genotype and fibrosis stage

Nowadays, IFN-free regimens represent the best options in treatment-naïve and treatment-experienced patients with HCV-related chronic hepatitis, compensated and decompensated liver disease, because of their excellent virologic efficacy, safety, tolerability, short duration and ease of use. Individualized indications depend on the HCV genotype/subtype, severity of liver disease, the response to prior antiviral therapy, potential DDIs and the presence of specific groups or conditions.

Having this landscape, SRGH recommends the *principle of cost-efficiency* when choosing the antiviral regimen for a defined group of HCV-infected patients. The most cost-effective regimen should be chosen to maximize the number of patients who can be successfully treated. As there is no statistically significant difference in relative efficacy among all oral regimens, then the cheapest treatment is likely to be the most cost-effective. The cost of the drug is the subject of negotiations between drug companies and the National Insurance Agency and it is expected that the cheapest regimen will be completely reimbursed.

The current recommendations by genotype, for patients without and with compensated (Child-Pugh A) and decompensated (Child-Pugh B and C) cirrhosis are summarized in Tables IV, V and VI.

### 8.1. Treatment of GT-1 infected patients without or with compensated cirrhosis

Five DAAs regimens are available in 2017 for treating GT-1 infected patients with or without compensated cirrhosis [24, 33].

***Sofosbuvir/Ledipasvir FDC***

GT-1 infected patients with or without compensated cirrhosis can be treated with Sofosbuvir/Ledipasvir FDC (400 mg plus 90 mg, respectively) one pill per day [A1]. Treatment-naïve patients should receive the FDC Sofosbuvir/Ledipasvir for 12 weeks without Ribavirin [A1]. Treatment can be shortened to 8 weeks in treatment-naïve patients without cirrhosis, if they have a baseline HCV RNA below 6 million (6.8 $\log_{10}$) IU/ml; this recommendation should be considered with caution in F3 patients [B1]. Treatment-experienced patients (DAA-naïve) infected with GT-1b should be treated with the FDC Sofosbuvir/Ledipasvir for 12 weeks without Ribavirin [A1]. Treatment-experienced patients (DAA-naïve) infected with GT-1a should be treated with the FDC Sofosbuvir/Ledipasvir for 12 weeks with Ribavirin (1000 or 1200 mg, according to body weight)[A1]. Treatment-experienced DAA-naïve patients infected with GT-1a with contraindication/intolerance to ribavirin should receive the FDC Sofosbuvir/Ledipasvir for 24 weeks without Ribavirin [B1].

These recommendations are based on the results of the four phase III RCTs ION-1, ION-2, ION-3 and ION-4 [47-49], on several post-hoc analyses of pooled data from phase II and III RCTs [50, 51], as well as on several real-world observational studies [52-54].

***Sofosbuvir/Velpatasvir FDC***

GT-1 infected patients, either treatment-naïve or treatment-experienced, with or without compensated cirrhosis can be treated with the FDC Sofosbuvir/Velpatasvir (400 mg plus 100 mg, respectively) in a single pill administered once per day for 12 weeks without Ribavirin [A1].

The recommendation is based on the results of the phase III ASTRAL-1 trial in patients with HCV GT-1 infection (22% with compensated cirrhosis, 66% treatment-naïve, 34% treatment-experienced) [53].

***Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir***

GT-1 infected patients with or without compensated cirrhosis can be treated with the FDC Ritonavir/Paritaprevir/Ombitasvir (50 mg/75 mg/12.5 mg) in one single tablet plus Dasabuvir (250 mg). They should receive two tablets of FDC Ritonavir/Paritaprevir/Ombitasvir once daily (in the morning) with food, plus one tablet twice daily of Dasabuvir (in the morning and evening) [A1].

GT-1b infected patients with or without compensated cirrhosis should receive the combination for 12 weeks without Ribavirin [A1].

**Table IV.** IFN-free combinations available for treating HCV infection according to genotype (adapted from EASL Guidelines. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2017; 66: 153-194 )[24]

| Regimen | GT1 | GT2 | GT3 | GT4 | GT5 & 6 |
|---|---|---|---|---|---|
| SOF/LDV±RBV | Yes | No | No | Yes | Yes |
| SOF/VEL ±RBV | Yes | Yes | Yes | Yes | Yes |
| PrOD±RBV (3D±RBV) | Yes | No | No | No | No |
| PrO ±RBV | No | No | No | Yes | No |
| GZV/EBV±RBV | Yes | No | No | Yes | No |
| SOF/DAC ±RBV | Yes | Yes | Yes | Yes | Yes |
| SOF/SIM±RBV | Suboptimal | No | No | Yes | No |

GT: genotype; SOF: Sofosbuvir; LDV: Ledipasvir; RBV: Ribavirin; VEL: Velpatasvir; PrOD: Paritaprevir/ritonavir/Ombitasvir plus Dasabuvir; PrO: Paritaprevir/ritonavir/Ombitasvir; GZV: Grazoprevir; EBV: Elbasvir; DAC: Daclatasvir; SIM: Simeprevir.

**Table V.** Treatment recommendations for HCV infected patients with chronic hepatitis C without cirrhosis, treatment-naïve and treatment-experienced to Pegylated IFN-α and Ribavirin (DAA-naïve) patients (adapted from EASL Guidelines. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2017; 66: 153-194) [24]

| GT | TN or TE | Sofosbuvir + Ledipasvir | Sofosbuvir + Velpatasvir | Sofosbuvir + Simeprevir | Sofosbuvir + Daclatasvir | Ombitasvir + Paritaprevir + Ritonavir + dasabuvir | Grazoprevir/ elbasvir |
|---|---|---|---|---|---|---|---|
| 1a | TN | 8-12 wk, no Ribavirin | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin | 12 wk, with ribavirin | 12 wk, no ribavirin if HCV RNA ≤800,000 (5.9$\log_{10}$) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 $\log_{10}$) IU/ml |
| | TE | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | |
| 1b | TN | 8-12 wk, no Ribavirin | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin | 8-12 wk, no Ribavirin | 12 wk, no Ribavirin |
| | TE | 12 wk, no Ribavirin | | | | 12 wk, no Ribavirin | |
| 2 | TN and TE | NR | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin | NR | NR |
| 3 | TN | NR | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin | NR | NR |
| | TE | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | |
| 4 | TN | 12 wk, no Ribavirin | 12 wk, no Ribavirin | 12 wk, no ribavirin | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin |
| | TE | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | 12 wk with Ribavirin or 24 wk no Ribavirin | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | 12 wk, no Ribavirin if HCV RNA ≤800,000 (5.9 $\log_{10}$) IU/ml or 16 wk with Ribavirin if HCV RNA >800,000 (5.9 $\log_{10}$) IU/ml |
| 5 or 6 | TN | 12 wk, no Ribavirin | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin | NR | NR |
| | TE | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | |

GT: genotype; NR: not recommended; TN: treatment-naïve; TE: treatment-experienced; wk: weeks.

GT-1a infected patients without compensated cirrhosis should receive the combination for 12 weeks with Ribavirin (1000 or 1200 mg, according to body weight <75 kg or ≥75 kg, respectively) [A1], whereas GT-1a infected patients with compensated cirrhosis should receive 3D combination for 24 weeks with daily weight-based Ribavirin (1000 or 1200 mg, according to body weight) [A1].

Treatment-naïve GT-1b infected patients without cirrhosis can receive the FDC Ritonavir/Paritaprevir/Ombitasvir plus Dasabuvir for 8 weeks without Ribavirin; caution is recommended for F3 patients [B1].

These recommendations are based on the results of 10 phase III RCTs designed as proof-of-concept for various hypotheses and defined groups of patients: SAPPHIRE-1 and 2, PEARL-1 to 4, MALACHITE-1 and 2, TURQUOISE 1 and 2 [55-60].

***Grazoprevir/Elbasvir FDC***

Treatment-naïve and treatment-experienced GT-1b infected patients with or without compensated cirrhosis can be treated with the FDC Grazoprevir/Elbasvir for 12 weeks without Ribavirin [A1].

If NS5A resistance testing cannot be performed, treatment-naïve and treatment-experienced GT-1a infected patients without/with compensated cirrhosis showing a baseline HCV RNA >800,000 IU/ml (5.9 $\log_{10}$ IU/ml) should receive the FDC Grazoprevir/Elbasvir for 16 weeks with Ribavirin (1000 or 1200 mg, according to body weight <75 kg or ≥75 kg, respectively); if baseline HCV RNA level is ≤800,000 IU/ml (5.9 $\log_{10}$ IU/ml), the combination should be administered for 12 weeks without Ribavirin [B1].

If reliable NS5A resistance testing can be performed, treatment-naïve and treatment-experienced GT-1a infected patients with or without compensated cirrhosis should receive the FDC Grazoprevir/Elbasvir for 16 weeks with Ribavirin (1000 or 1200 mg, according to body weight <75 kg or ≥75 kg, respectively) if their baseline HCV RNA is >800,000 IU/ml (5.9 $\log_{10}$ IU/ml) and NS5A RASs that confer resistance to Elbasvir (M28A/G/T, Q30D/E/G/H/K/L/R, L31F/M/V, H58D and/or Y93C/H/N/S) are present at baseline. GT-1a infected patients with HCV RNA ≤800,000 IU/ml (5.9 $\log_{10}$ IU/ml) at baseline and those with HCV RNA >800,000 IU/ml (5.9 $\log_{10}$ IU/ml), but without NS5A RASs at baseline should receive the FDC Grazoprevir/Elbasvir for 12 weeks without Ribavirin [B1].

**Table VI.** Treatment recommendations for HCV infected patients with chronic hepatitis C and cirrhosis, treatment-naïve and treatment-experienced to Pegylated IFN-α and Ribavirin (DAA-naïve) patients (adapted from EASL Guidelines. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2017; 66: 153-194) [24]

| GT | TN or TE | Sofosbuvir + Ledipasvir | Sofosbuvir + Velpatasvir | Sofosbuvir + Simeprevir | Sofosbuvir + Daclatasvir | Ombitasvir + Paritaprevir + Ritonavir + dasabuvir | Grazoprevir/ elbasvir |
|---|---|---|---|---|---|---|---|
| 1a | TN | 12 wk, no Ribavirin | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin | 24 wk, with Ribavirin | 12 wk, no Ribavirin if HCV RNA ≤800,000 (5.9 $\log_{10}$) IU/ml or 16 wk with Ribavirin if HCV RNA >800,000 (5.9 $\log_{10}$) IU/ml |
| | TE | 12 wk, with Ribavirin Or 24 wk, no Ribavirin | | | 12 wk, with Ribavirin Or 24 wk, no ribavirin | | |
| | DC | 12 wk, with Ribavirin or 24 wk, no Ribavirin | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | NR | NR |
| 1b | TN | 12 wk, no Ribavirin | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin | 12 wk, no Ribavirin | 12 wk, no Ribavirin |
| | TE | | | | | | |
| | DC | 12 wk, with Ribavirin or 24 wk, no Ribavirin | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | NR | NR |
| 2 | TN and TE | NR | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin | NR | NR |
| | DC | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | |
| 3 | TN | NR | 12 wk, no Ribavirin | NR | 24 wk, with Ribavirin | NR | NR |
| | TE | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | | | |
| | DC | | 24 wk, with Ribavirin or 24 wk, no Ribavirin | | 24 wk, with Ribavirin or 24 wk, no Ribavirin | | |
| 4 | TN | 12 wk, no Ribavirin | 12 wk, no Ribavirin | 12 wk, no Ribavirin | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin |
| | TE | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | 12 wk with ribavirin or 24 wk no ribavirin | 12 wk, with Ribavirin Or 24 wk, no Ribavirin | | 12 wk, no Ribavirin if HCV RNA ≤800,000 (5.9 $\log_{10}$ IU/ml or 16 wk with Ribavirin if HCV RNA >800,000 (5.9 $\log_{10}$) IU/ml |
| | DC | 12 wk, with Ribavirin Or 24 wk, no Ribavirin | 12 wk, with Ribavirin Or 24 wk, no Ribavirin | NR | 12 wk, with Ribavirin Or 24 wk, no Ribavirin | | NR |
| 5 or 6 | TN | 12 wk, no Ribavirin | 12 wk, no Ribavirin | NR | 12 wk, no Ribavirin | NR | NR |
| | TE | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | |
| | DC | 12 wk, with Ribavirin or 24 wk, no Ribavirin | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | 12 wk, with Ribavirin or 24 wk, no Ribavirin | | |

GT: genotype; NR: not recommended; TN: treatment-naïve; TE: treatment-experienced; DC: decompensated cirrhosis.

These recommendations are based on the results of three phase III RCTs (C-EDGE-TN, C-EDGE-TE, C-EDGE-Coinfection) [61, 62] and a post-hoc analysis of pooled phase II and III clinical trials data [63].

***Sofosbuvir and Daclatasvir***

Patients infected with HCV GT-1 can be treated with the combination Sofosbuvir (400 mg) in one tablet and Daclatasvir

(60 mg) in one tablet; the two tablets containing regimen should be administered once daily [A1].

Treatment-naïve patients with or without compensated cirrhosis should be treated for 12 weeks without Ribavirin [A1].

Treatment-experienced (DAA naïve) GT-1b with or without compensated cirrhosis should be treated for 12 weeks without Ribavirin [A1].

Treatment-experienced (DAA naïve) GT-1a with or without compensated cirrhosis should be treated for 12 weeks with daily weight-based Ribavirin (1000 or 1200 mg, according to body weight <75 kg or ≥75 kg, respectively); evidence quality and strength of this recommendation is weak, resulting by equivalence with a Sofosbuvir/Ledipasvir combination [C2].

If reliable NS5A resistance testing can be performed, treatment-experienced (DAA naïve) GT-1a infected patients with or without compensated cirrhosis with NS5A RASs detected at baseline should receive the combination Sofosbuvir 400 mg plus Daclatasvir 60 mg daily for 12 weeks with Ribavirin (1000 or 1200 mg, according to body weight <75 kg or ≥75 kg, respectively), whereas those without NS5A RASs detected at baseline should receive the combination for 12 weeks without Ribavirin [C2].

Patients with contraindication/intolerance to Ribavirin should receive the combination of Sofosbuvir and Daclatasvir for 24 weeks without Ribavirin [B1].

The dose of Daclatasvir must be adjusted to 30 mg in HIV co-infected patients receiving Efavirenz or pharmacokinetic enhancers that inhibit the CYP3A system (Ritonavir- or Cobicistat-boosted Atazanavir or Cobicistat-boosted Elvitegravir) [B1].

These recommendations are based on the results of phase IIb and III RCTs [64, 65].

As HCV infection with other genotypes than GT-1 is rarely seen in Romanian patients, the treatment of patients without or with compensated cirrhosis infected with GT-2, GT-3, GT-4 and GT-5-6 (**chapters 8.2-8.5**) can be found only in the electronic version of the Position Paper.

The **chapters 9-14** of this Position Paper (see Methodology) will be published in the next issue (volume 26, number 3, September 2017) of the journal.

## CONCLUSIONS

This position paper represents a guide for the assessment and the therapy of HCV infection. The recommendations are in concordance with other guidelines but are applied to the real-life conditions in this country.

**Conflicts of interest:** There are no conflicts of interest regarding this paper.

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