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Position Paper on Treatment of Hepatitis C in Romania 2017. Part Two

Liana Gheorghe[1], Ioan Sporea[2], Speranța Iacob[1], Roxana Șirli[2], Anca Trifan[3], Mircea Diculescu[1], Carol Stanciu[3], Oliviu Pascu[4], Monica Acalovschi[4], Ciprian Brisc[5], Cristina Cijevschi[3], Cristian Gheorghe[1], Zeno Spârchez[4], Ion Rogoveanu[6], Daniela Dobru[7], Dan L. Dumitrascu[8]

1) Center for Digestive Diseases and Liver Transplantation, Fundeni Clinical Institute, Carol Davila University of Medicine and Pharmacy, Bucharest; 2) Department of Gastroenterology and Hepatology, Victor Babeș University of Medicine and Pharmacy, Timișoara; 3) Institute of Gastroenterology and Hepatology, Grigore T. Popa University of Medicine and Pharmacy, Iasi; 4) 3rd Medical Clinic, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca; 5) Gastroenterology Department, Faculty of Medicine and Pharmacy, Oradea; 6) Gastroenterology Department, University of Medicine and Pharmacy, Craiova; 7) Gastroenterology Department, University of Medicine and Pharmacy, Târgu Mureș; 8) 2nd Medical Clinic, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Address for correspondence:
Speranta Iacob
Center for Digestive Diseases and Liver Transplantation, Fundeni Clinical Institute, Bucharest, Romania
msiacob@gmail.com

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*Society of Gastroenterology and Hepatology

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 have become 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 was created and these were discussed and rated. Decisions were taken by consensus.

Recommendations: We present here the second part of the Society's recommendations for chronic HCV infection treatment. An agreement between experts was reached regarding the therapy of the special categories of patients infected with HCV, complications and monitoring of the therapy, follow-up of the patients who reached sustained virologic response and re-treatment of the patients with therapy failure.

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 real-life conditions in Romania.

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

Abbreviations: CKD: Chronic kidney disease; DAAs: Direct-acting antivirals; DDIs: Drug-drug interactions; ESDL: End-stage liver disease; FCH: Fibrosing cholestatic hepatitis; GT: Genotype; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; LT: Liver transplantation; MELD score: Mayo-Clinic End-Stage Liver Disease score; PDC: Premature discontinuation; PWID: Persons who inject drugs; RASs: Resistance associated substitutions; RBV: Ribavirin; RCT: Randomized controlled trial; SAE: Serious adverse events; SRGH: Romanian Society of Gastroenterology and Hepatology; SVR: Sustained virologic response.

INTRODUCTION

Hepatitis C virus (HCV) infection is a common condition with an endemic prevalence in some areas of the world. New treatments have become available on the market in recent years and new drugs are in development. A re-evaluation of HCV therapy was considered mandatory. The Romanian Society of Gastroenterology and Hepatology undertook this task for the practitioners from Romania, a country with a mean prevalence of HCV infection of about 3%.

The *Position Paper* has been prepared by a panel of experts appointed by the Board of the Romanian Society of Gastroenterology and Hepatology (SRGH). It has been based on evidence-based data, international guidelines in the field and the local expertise in the management of HCV infection. The first part of the SRGH Position Paper, including the Methodology of elaborating the Recommendations for the treatment of chronic HCV infection was published in the previous issue of the *J Gastrointestin Liver Dis* (June 2017) [1]. This second part of the SRGH Position Paper includes the following six chapters: special therapeutic groups of chronic HCV infection; therapeutic monitoring and response assessment; dose reduction and treatment discontinuation;

support measures/programs aiming to improve access, adherence and efficacy of therapy; follow-up of patients who achieved sustained virologic response (SVR), and re-treatment of patients with treatment failure.

KEY RECOMMENDATIONS (continued)

9. Special therapeutic groups of chronic HCV infection

9.1. Treatment of patients with decompensated cirrhosis with/without hepatocellular carcinoma (HCC), with/without indication of liver transplantation (LT)

9.1.1. Patients with decompensated cirrhosis, without HCC, awaiting LT

There is an on-going debate whether patients with decompensated cirrhosis (Child Pugh score B and C up to 12 points) on the transplant waiting list should receive antiviral treatment before LT or right after LT. So far, no consensus has been established because there are no prospectively compared and appropriately powered randomized trials (RCTs) in this regard and it is unlikely that such trials will be performed [2]. Thus, the recommendations are based on the results of clinical trials assessing each approach, data coming from the real world and the experts' experience.

The general recommendations made by the expert group of the SRGH in this category of difficult-to-treat patients are as follows:

- Patients with decompensated HCV cirrhosis awaiting LT can be treated with direct-acting antivirals (DAAs) before LT, if the MELD score is ≤18-20 [3]. In daily clinical practice in our country, a case by case judgement is recommended, as this cut-off of MELD score was arbitrarily set [2]. Patients with HCV decompensated cirrhosis should be referred to a gastroenterologist with expertise in anti-HCV therapy and taking care of patients with end-stage liver disease (ESLD), ideally in a transplant center. Treatment should be initiated as soon as possible in order to complete a full treatment course and achieve SVR before LT [3, 4]. A benefit of SVR may be a significant improvement of liver function, leading to temporary inactivation or even delisting of selected cases [5, 6] [B1];

- Treatment regimens including an NS3/4A protease inhibitor, such as Simeprevir, ritonavir-boosted Paritaprevir or Grazoprevir, are contraindicated in patients with Child-Pugh B and C decompensated cirrhosis and in compensated cirrhosis with previous episodes of decompensation, because of the substantially higher protease inhibitor exposure in these patients [A1];

- Only Sofosbuvir-based regimens are recommended: 1) Sofosbuvir plus Ledipasvir, 2) Sofosbuvir plus Daclatasvir, or 3) Sofosbuvir plus Velpatasvir with daily weight-based ribavirin (RBV) (1000 or 1200 mg if body weight is <75 kg or >75 kg, respectively). RBV should be initiated at a low dose of 600 mg per day, increased subsequently depending on patient's tolerability [A1];

- We recommend frequent clinical and laboratory monitoring in a center with capability and expertise in managing decompensated cirrhotics [B2] [2, 3].

Patients infected with genotype (GT) 1, 4, 5, and 6 can be treated with Sofosbuvir plus Ledipasvir, Sofosbuvir plus Daclatasvir or Sofosbuvir plus Velpatasvir for 12 weeks, with daily weight-based RBV [A1]. In GT 2 and 3 patients, the recommended regimens are Sofosbuvir plus Daclatasvir or Sofosbuvir plus Velpatasvir for 12/24 weeks with RBV [B1]. Patients with contraindications or intolerance/poor tolerance to RBV should be treated with the previously enumerated regimens for 24 weeks without RBV [B1].

Patients with a MELD score >18-20 in LT programs where the waiting time to transplant exceeds 6 months can be treated cautiously before LT [B1] [2, 3].

Most of these recommendations have been documented in SOLAR 1 and 2 [7, 8], ALLY-1 [9] and ASTRAL-4 [10] RCTs, as well as in real-world studies [11].

9.1.2. Patients with decompensated cirrhosis without HCC and without indication for LT

The main goal of anti-HCV therapy in patients with decompensated cirrhosis (Child Pugh class B and C) who are not on a transplant waiting list is to eradicate HCV infection and, subsequently, to improve liver function and survival [5, 8-11]. Patients with Child-Pugh B cirrhosis benefit more from viral clearance in terms of liver events-free survival at 15 months than those with Child-Pugh C cirrhosis [11].

Considering the existing data, our recommendation is to treat decompensated cirrhosis without HCC but not on the waiting list for LT immediately, if they have no comorbidities that may impact their short-term life expectancy. The same DAAs combinations and duration of therapy, with [A1] or without [B2] RBV as in patients with decompensated cirrhosis awaiting LT are recommended, under frequent clinical and laboratory monitoring performed in expert centers [A1].

9.1.3. Patients with decompensated cirrhosis and HCC

Patients with decompensated cirrhosis and HCC awaiting LT should receive antiviral therapy as soon as possible in order to complete the full course of therapy and obtain SVR before LT [B1]. The recommended DAAs regimens and duration of therapy, with [A1] or without [B2] ribavirin, do not differ from those recommended in patients with decompensated cirrhosis and no HCC.

In our opinion, patients with decompensated cirrhosis and HCC, without indication for LT or delisted due to the initially advanced state or the progression of their tumor(s) should not receive antiviral therapy, due to futility and unknown impact on tumor progression [B2]. Patients undergoing curative therapy for HCV-associated HCC (resection or ablation) should receive appropriate antiviral therapy (preferably after HCC therapy), according to the HCV genotype, unless further studies will prove a harmful effect, especially on the recurrence rate [B2] [12-17]. As the recurrence rate of HCC after resection or ablation therapy is quite high (12-15% and 25-30%, respectively), a high-quality contrast dynamic CT or MRI assessment is recommended before treatment initiation [B2]. We also recommend to postpone antiviral therapy at least 24 weeks after curative resection or ablation, in order to observe tumor behavior and avoid futile therapy in patients with aggressive HCC, progressing rapidly beyond eligibility criteria for LT [B2].

9.2. Treatment of patients with recurrence of HCV infection after liver transplantation

Recurrent hepatitis C of the graft is a major cause of morbidity and mortality after LT. The course of recurrent HCV infection is accelerated in LT recipients, approximately one third of them developing cirrhosis within 5 years after LT [18, 19].

Thus, the recommendations for antiviral therapy in LT recipients, made by the group of SRGH experts are as follows:

- Antiviral therapy with DAAs should be initiated in all patients with HCV recurrent infection after LT, irrespective of presence of inflammation and/or fibrosis [A1] [3, 4];

- Patients with recurrent HCV infection following LT must be treated by an expert gastroenterologist-hepatologist in a transplant center [A1];

- Our recommended approach is to start antiviral therapy after the first 3 to 6 months following LT, when the immunosuppressive agents are tapered and the trough levels become stable [A1] [3, 4, 20];

- In patients with fibrosing cholestatic hepatitis (FCH), moderate to extensive fibrosis or portal hypertension one year after LT, antiviral therapy with DAAs should be initiated immediately due to the risk of rapid progression and graft loss [A1]] [3, 20-25];

- Also, in cases of overlap or unclear differential diagnosis between acute cellular rejection and recurrent hepatitis C, antiviral therapy with DAAs can be taken into consideration [A2] [25].

The recommended antiviral regimens in the post-transplant setting include the following [3, 4, 7-9, 25-28]:

- Patients with recurrent hepatitis C GT-1, 4, 5 and 6 without cirrhosis (F0-F3), with compensated (Child A) or decompensated (Child B and C) cirrhosis should be treated with: 1) the fixed dose combination Sofosbuvir plus Ledipasvir [30-33] or 2) the combination of Sofosbuvir plus Daclatasvir [3, 9, 34] for 12 weeks with daily weight based RBV (1000mg or 1200mg/day in patients <75kg or ≥75 kg, respectively), without the need of adjustments in the immunosuppression regimen (exception for everolimus)[A1];

- Patients with recurrent hepatitis C GT-2 or 3 without cirrhosis (F0-F3), with compensated (Child A) or decompensated (Child B/C) cirrhosis should be treated with the combination of Sofosbuvir plus Daclatasvir for 12/24 weeks with daily weight-based RBV (1000mg or 1200mg/day in patients <75kg or ≥75 kg, respectively) [3, 9, 34], without the need of adjustments in the immunosuppression regimen (exception for everolimus) [B1];

- All HCV-infected patients, irrespective of HCV GT or stage of the liver disease, could be treated with the fixed-dose combination of Sofosbuvir plus Velpatasvir for 12 weeks or 24 weeks (only in GT-3 and decompensated Child B and C cirrhosis) with daily weight-based RBV (1000mg or 1200mg/day in patients <75kg or ≥75 kg, respectively) [3] [C2] (results of on-going studies are awaited in order to increase the quality of evidence and the strength of this recommendation, as well as data on DDIs of this regimen with immunosuppressive drugs);

- Patients with GT-1 and F0-F3 fibrosis or compensated Child A cirrhosis can be treated with the combination of ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir plus RBV (1000mg or 1200mg/day in patients <75kg or ≥75 kg, respectively) for 24 weeks [2, 27, 35] [B1]. Due to drug-drug interactions (DDIs) of Ritonavir and Paritaprevir with tacrolimus and cyclosporine, dose reduction (cyclosporine at 20% of previous stable daily dose and tacrolimus 0.5 mg at 7-14 days interval) and frequent monitoring of immunosuppressive drugs is recommended. This combination can be used also in LT recipients with associated renal failure with a GFR <30 and >15ml/min; this combination should not be used in association with everolimus/sirolimus [B1].

So far, no data with the fixed-dose combination of Grazoprevir and Elbasvir in LT recipients have been reported. Interactions with immunosuppressive drugs that require dose adjustments have been reported; in addition, this combination is contraindicated in patients receiving cyclosporine.

Patients with contraindications or intolerance/poor tolerance to RBV should be treated with the previously enumerated regimens for 24 weeks without RBV [B1]. Whether RBV use is mandatory in post-LT patients without cirrhosis or with compensated Child A cirrhosis remains to be demonstrated in further studies [C2].

In case of decompensated graft cirrhosis, antiviral therapy could be administered on an individual case by case judgement, considering increasing duration of therapy to 24 weeks and starting RBV at a low dose (400-600mg/day) [B1].

9.3. Non-hepatic solid organ transplant recipients (e.g. kidney/heart/lung/pancreas/small bowel)

HCV infection in kidney transplant recipients is associated with an increased risk of liver disease progression. On the other hand, HCV positivity is associated with impaired kidney graft survival and increased patient mortality, particularly if liver cirrhosis has been developed [36, 37]. Data on impact of HCV infection after heart or lung transplantation are scarce and controversial, with studies reporting decreased survival in HCV positive recipients. No data are available about the impact of HCV infection and its therapy in pancreas or small bowel recipients. Experience with DAAs therapy in liver transplant recipients suggests that these patients can be treated with anticipated high SVR rates and acceptable safety and tolerability. Thus, solid organ transplantation does not represent any more a contraindication for HCV treatment in the DAAs era.

All non-hepatic solid organ recipients, including kidney, heart, lung, pancreas or small bowel recipients, should receive DAAs therapy after transplantation in case of positive HCV RNA, irrespective of liver fibrosis and as soon as possible (usually after 3 to 6 months), provided that their life expectancy exceeds one year [A1] [38-42].

Also, listing of HCV positive candidates for kidney/heart/lung transplantation is no longer a contraindication because antiviral therapy can also be administered on the waiting list [A1] [43, 44]. The decision of treating these patients before or after solid-organ transplantation is weighted individually [A2]

The following antiviral regimens are indicated post-kidney/cardiac/pulmonary/pancreas/small bowel transplantation [2, 3, 41, 45-47]:

- Patients with GT-1, 4, 5, 6 HCV infection should be treated with: 1) the fixed dose combination Sofosbuvir and Ledipasvir, 2) the fixed-dose combination of Sofosbuvir and Velpatasvir (if the DDI profile with immunosuppressants will be shown as favorable in on-going studies), or 3) the combination of Sofosbuvir plus Daclatasvir for 12/24 weeks, with/without weight-based RBV, according to the general recommendation, without the need of adjustments in the immunosuppressant regimen (exception for everolimus) [B1];

- Patients with GT-2 and 3 HCV infection should be treated with: 1) the fixed-dose combination of Sofosbuvir and Velpatasvir (if the drug-drug interaction profile with immunosuppressant will be shown as favorable in on-going studies) or 2) the combination of Sofosbuvir plus Daclatasvir for 12 or 24 weeks, with/without weight-based RBV [B1].

Similar to LT, DDIs with immunosuppression agents should be taken into account and monitored during therapy [A1]. Rejection after the end of antiviral therapy and viral clearance should be closely followed-up due to improvement of liver function and immunosuppression metabolism [A2] [38, 44].

9.4. Patients with chronic kidney disease, including hemodialysis patients

HCV infection is highly prevalent in patients with chronic kidney disease (CKD) and hemodialysis patients. In these groups of patients, HCV infection is associated with increased risk of all-cause and liver-related mortality, with cardiovascular events remaining the main cause of death. For these reasons, antiviral therapy should be considered for all HCV positive patients with CKD. Based on severity of renal impairment, diverse groups of patients with CKD require specific consideration for HCV treatment.

In HCV positive patients with mild to moderate renal impairment (eGRF≥30 ml/min/1.73m^2), dose adjustments are neither necessary for Sofosbuvir-based regimens, nor for the combination ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir or Grazoprevir and Elbasvir. These patients should therefore be treated according to the general recommendations and carefully monitored [A1].

Patients with severe CKD (eGRF<30 ml/min/1.73m^2) and patients with end-stage renal disease (ESRD) on hemodialysis, should be treated with Sofosbuvir-free regimens, whenever possible in expert centers and carefully monitored by a multidisciplinary team [B1].

Sofosbuvir-based regimens should be avoided in patients with severe CKD (eGRF<30 ml/min/1.73m^2) and patients with ESRD as data on the safety and efficacy are lacking and no dose recommendations can currently be given for these patients [B1]. Sofosbuvir-based regimens in severe CKD stage 4 or 5 or in hemodialysis patients are currently out the license recommendations. Sofosbuvir and its metabolite GS-331007 are eliminated mainly by renal route and they can reach therefore substantially high plasma concentration [48]. In the TARGET 2.0 real-world cohort study, progressive deterioration of renal function and renal symptoms were reported in patients with severe renal disease receiving Sofosbuvir-based regimens [49].

In patients with HCV infection and severe CKD stage 4/5 (eGFR<30 mL/min/1.73 m^2) or ESRD on hemodialysis with indication for renal transplantation, the individual assessment of risks and benefits of treating them before or after renal transplantation, should be carefully considered [B2].

In patients with HCV infection and severe CKD stage 4/5 (eGFR<30 mL/min/1.73 m^2) or ESRD on hemodialysis in whom urgency to treat is high and renal transplant is not an immediate option, the following antiviral regimens are indicated:

- GT-1b patients should be treated with the combination ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir [1, 2, 42] or Grazoprevir and Elbasvir [2, 3, 44] for 12 weeks, without RBV [A1];

- GT-1a patients in whom hemoglobin level is >10g/dL at baseline [B1] should be treated with the same combinations and additionally RBV 200mg/day or ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir for 24 weeks [2, 3, 43, 44];

- GT-4 patients should receive the combination ritonavir-boosted Paritaprevir and Ombitasvir for 12 weeks with daily RBV (200mg/day) if the hemoglobin level is >10g/dL at baseline or the combination Grazoprevir and Elbasvir for 12 weeks without RBV [B1];

- only if treatment is urgently needed in GT-2/3 patients these patients could receive therapy with a Sofosbuvir-containing regimen [2] as follows: the fixed-dose combination Sofosbuvir and Velpatasvir or the combination Sofosbuvir and Daclatasvir for 12 weeks without RBV (GT-2) or the same combinations with RBV (200mg/day) if the hemoglobin level is >10g/dL at baseline or without RBV for 24 weeks (GT-3) [B1].

Individualized Ribavirin dosing of 200 mg/day, 200 mg/every other day or 200 mg thrice weekly after hemodialysis or avoiding RBV and increasing the duration of therapy is recommended in patients with severe CKD or ESRD. Hemoglobin levels should be carefully and frequently monitored, stopping RBV in case of anemia with hemoglobin < 8.5g/dl. Use of erythropoietin or blood transfusions, if necessary, may be useful [B1].

9.5. Patients with HBV-HCV coinfection

In patients with HBV-HCV coinfection, HBV DNA levels are usually low or undetectable, HCV being the leading cause of liver injury. However, there is a potential and unpredictable risk of HBV reactivation during or after HCV clearance with DAAs regimens, although it is low in our experience.

If HBs antigen is positive or HBV DNA is detectable in HBs antigen negative-anti-HBc positive patients (occult infection), concurrent HBV therapy with nucleoside/nucleotide analogues can be considered [B1]. Alternatively, careful and frequent aminotransferase levels monitoring is recommended for patients with concomitant HBV chronic or occult infection, starting nucleos/tide (NUC) therapy in case of signs of reactivation.

Patients with HBV-HCV coinfection should be treated with the same regimens as monoinfected patients [B1].

9.6. Patients with immune-mediated manifestations of chronic hepatitis C

Several systemic immune complex-mediated manifestations of chronic HCV infection have been described: mixed

cryoglobulinemia, chronic renal disease (in context of type I membrano-proliferative glomerulonephritis, vasculitic involvement or interstitial nephritis) and B cell non-Hodgkin lymphoma. Recent studies suggested that achieving SVR by interferon-free regimens, at least in mixed cryoglobulinemia and immune-mediated renal disease, in association with standard-of-care (immunosuppressive therapy, Rituximab, plasma exchange etc.), can improve the outcome of these patients.

Therefore, antiviral therapy should be considered for HCV positive patients with mixed cryoglobulinemia and immune-mediated renal disease, according to general recommendations. During therapy, patients should be carefully monitored for adverse events [B1]. In HCV-associated B cell lymphoma, DAA treatment is appropriate, but the impact of SVR on the overall prognosis of these patients remains to be documented [B1].

9.7. Hemoglobinopathies and bleeding disorders

The most frequent hemoglobinopathies associated with HCV chronic infection are thalassemia and sickle cell anemia requiring frequent blood transfusions and leading to an accelerated course of liver disease because of the concurrent iron overload. High SVR rate (95-98%) with good safety and tolerability has been reported in patients with sickle cell anemia or β-thalasemia in the C-EDGE IBLD study [50]. The indications and regimens of anti-HCV therapy are the same in patients with and without hemoglobinopathies [A1] apart from the fact that they should be treated without RBV [B1]. If RBV is needed, careful monitoring is recommended, and blood transfusion support may be required [B2].

In inherited bleeding disorders such as hemophilia, the management of chronic HCV infection is similar to the non-hemophilic population (indications, regimens) [A1] and DAAs therapy is associated with high SVR rates (91%) [50].

9.8. Persons who inject drugs (PWID) and patients on stable maintenance substitution

The general prevalence of HCV infection among PWIDs is approximately 65% and >80% in long-term drug users. Therefore, PWIDs should be routinely tested for HCV infection and, if negative, annual testing is recommended due to the increased risk of infection and reinfection [A1] [2, 3].

Complex strategies including screening, linkage to care and antiviral therapy together with harm reduction support programs are urgently required for this important reservoir of HCV-infected individuals. PWIDs should receive antiviral therapy not only for reducing the individual harmful effect of HCV infection on the outcome of these subjects, but also in order to reduce HCV transmission. Most DAAs clinical development programs have excluded active drug users, but many trials have included PWIDs on opioid substitution therapy. The SVR rates in these patients was high (92-97%), adherence to medication was high and safety did not differ from that in non-PWIDs [2, 3, 51, 52].

HCV therapy must be considered for all PWIDs who are willing to receive therapy, to maintain adherence and frequent monitoring, and accept to enter in dedicated programs of integrated management of substance abuse and harm reduction (syringe exchange program, substitution therapy, social and psychiatric support, etc.) [A1]. PWIDs should be provided with antiviral therapy on an individualized case-by-case basis, within a multidisciplinary team setting [A1].

In PWIDs, pre-therapeutic assessment should include also education and counselling consisting of discussions about HCV transmission, risk factors for fibrosis progression, cultural issues, familial and social support, finances, nutrition, drug and alcohol use, treatment, risk of reinfection, linkage to harm reduction programs [A1]. Antiviral regimens for treating PWIDs are the same as in non-PWIDs. There is no need for methadone or buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be performed [B1]. DDIs between DAAs and opioid substitution therapy, antidepressants, antipsychotics and sedatives frequently used by subjects with addiction problems have been studied and careful monitoring is recommended, especially for opioid or psychoactive drugs toxicity.

10. Therapeutic monitoring and response assessment

Therapeutic monitoring includes 1) monitoring of treatment efficacy and 2) monitoring for safety and DDIs at specific time points during therapy.

10.1. Monitoring treatment efficacy

As no guided therapy or stopping rules are recommended with current DAA regimens, efficacy of therapy should be assessed by measuring HCV RNA using a high sensitive molecular assay (LLD ≤ 15IU/ml) [A1] at 12 (SVR12) or 24 (SVR24) weeks after the end of therapy [A2]. Only optionally, HCV RNA can be assessed during therapy: between weeks 2 and 4 (for adherence assessment) and end-of therapy (to identify patients with breakthrough) [A2]. Treatment efficacy is defined as achieving sustained virological response (SVR) at 12 (SVR12) and/or 24 (SVR24) weeks after stopping therapy (see chapter 3 Position Paper on Treatment of Hepatitis C in Romania 2017 – Part one) [1].

10.2. Monitoring for safety and DDIs

New DAA regimens are significantly better tolerated than IFN-based therapy. Rates of adverse events and serious adverse events (SAE) leading to premature discontinuation (PDC) are generally low with IFN-free regimens (less than 2.5% and 1-2%, respectively). Despite this, SRGH expert group recommends that patients receiving IFN-free therapy should be assessed for adverse events, laboratory abnormalities and DDIs at each visit (at least monthly). Assessment at shorter intervals is recommended for patients who belong to special groups (decompensated cirrhosis, transplanted patients, renal impairment, specific co-morbidities, advanced age and multiple co-medications etc.) [A1].

ALT should be assessed monthly during therapy, at the end of treatment and then at 12 and 24 weeks post-treatment [A1].

Mild/moderate anemia can occur in RBV-containing DAA regimens. Therefore, hematological side effects should be assessed at 2 and 4 weeks of therapy, and monthly thereafter in patients receiving RBV [A1].

In patients receiving Sofosbuvir-based regimens (in combination with Ledipasvir, Daclatasvir or Velpatasvir), the most frequent adverse events are fatigue and headache. Renal function should be checked regularly, especially in those with impaired renal function [A1]. The use of Sofosbuvir is not recommended in patients with eGRF<30 ml/min/1.73 m^2[A1]. No dose adjustment of Sofosbuvir, Ledipasvir, Daclatasvir, Velpatasvir or Simeprevir is required in patients with renal impairment [B1].

The most common adverse events reported during therapy with Simeprevir in combination with Sofosbuvir are fatigue, headache, nausea, insomnia and pruritus. Monitoring for rash and indirect hyperbilirubinemia should be routinely performed in patients receiving Simeprevir-containing regimens [A1].

The most common adverse events in patients treated with the combination ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir (the 3D regimen) are fatigue, asthenia, nausea, insomnia and pruritus. Additionally, two main laboratory abnormalities have been noted: 1) symptomatic serum ALT elevation, occuring mainly in the first 4 weeks of therapy and spontaneously resolved, with no need of PDC and 2) transient increase in indirect bilirubin, related to the inhibition of bilirubin transporters OATP1B1 and OATP 1B3 by Paritaprevir, leading to hemolysis. Monitoring for indirect bilirubin elevation accompanied by rash and pruritus should be performed in patients receiving the 3D therapy [A1].

The most common adverse events observed in patients receiving Grazoprevir and Elbasvir are fatigue, headache and nausea. A rate of 0.8% of patients receiving this combination in phase II and III trials experienced asymptomatic ALT elevation up to >5 times the upper limit of normal, late in the course of Grazoprevir/Elbasvir therapy (at average 10 weeks after the start of therapy). Systematically ALT monitoring should be performed in these patients [A1].

In order to avoid potential harmful DDIs, a strong recommendation of the SRGH experts is to review all the drugs taken by the patient before initiating therapy, including over-the-counter compounds and recreational drugs, and to check potential interactions of concurrent drugs in regard of efficacy and safety. This is possible by checking systematically the site www.hep-druginteractions.org. Any interacting co-medication should be stopped for the duration of HCV therapy, when possible. When not, the patient should be switched to an alternative drug with less potential interaction or the dose should be modified [B1]]. The efficacy and toxicity of concurrent drugs given for co-morbidities and potential DDIs should be monitored during therapy by specific assay (e.g. Digoxin etc.) [A1].

11. Dose reduction and treatment discontinuation

In therapeutic regimens requiring RBV, the dose of RBV can be reduced stepwise by 200 mg/daily, if the hemoglobin levels drops <10 g/dl and stopped if the hemoglobin level drops <8.5 g/dl [A1].

No dose adjustments are recommended for DAAs [B1].

Treatment should be promptly stopped in case of hepatitis flare (ALT levels above 10 times normal) or in case of severe bacterial infections in any location and regardless of the neutrophil count, particularly in patients with decompensated cirrhosis [A1].

Any new sign/symptom should be carefully assessed. Treatment should be stopped in case of SAE of unclear origin or with unclear relationship with antiviral medication [B2].

12. Support measures/programs aiming to improve access, adherence and efficacy of therapy

IFN-free treatment for HCV infection should be delivered by a multidisciplinary team with experience in assessing and treating HCV patients, including gastroenterologist-hepatologist, psychologist/psychiastrist, virologist, pharmacist, HIV- and addiction specialists, dedicated nurses and additional specialists involved in the management of side effects [A1].

The SRGH expert group, based on previous experience in Romania, recommends the involvement of dedicated services and programs for medical and social support in the patients' care [A1].

Patients should be systematically counselled before and during therapy on the importance of adherence in achieving SVR [A1]. In addition, they should be counselled for a liver-healthy diet, to abstain from alcohol and to avoid herbal compounds and any un-necessary drug during therapy. A systematic review of prescribed and non-prescribed co-medication needs to be performed, and the potential harmful effect of DDIs should be highlighted [A1].

13. Follow-up of patients who achieved SVR

Non-cirrhotic patients who achieved SVR should be retested for HCV RNA and ALT eventually at 24 weeks post-treatment or once more after SVR12, then discharged if ALT is normal and HCV RNA undetectable and join the common healthcare programs ensured by primary physicians [A1].

SVR patients with advanced fibrosis (F3) and cirrhosis (F4) should be screened for HCC every 6 months by ultrasound [A1]. Guidelines for follow-up of liver function and portal hypertension should be implemented despite the fact that patients achieving SVR seldom show signs and symptoms of progression, unless additional causes for on-going liver injury are present, or if the disease was treated in a very advanced stage [A2].

In order to maximize the benefit of therapy, ongoing PWID who achieved SVR should be counselled on the risk of reinfection and positive behavioural modifications should be reinforced [A1]. However, in PWID and men who have sex with men (MSM) who achieved SVR with ongoing risk behavior, annual monitoring for HCV reinfection by HCV RNA assessment is recommended [A1].

14. Re-treatment of patients with treatment failure

Patients who failed after double combination PEG-IFN and RBV must be re-treated with an IFN-free regimen, according

to previous recommendations for "treatment-experienced" patients [A1].

Sofosbuvir is the single nucleoside inhibitor of HCV polymerase and has a high barrier to resistance. Clinical relevant HCV resistant variants to Sofosbuvir have been exceptionally reported and rapidly disappeared after treatment cessation [53, 54]. Therefore, retreatment strategies should include Sofosbuvir in the therapeutic regimen. On the contrary, patients previously exposed to a 2nd generation protease inhibitor (Paritaprevir, Grazoprevir, Simeprevir), a NS5A inhibitor (Ledipasvir, Daclatasvir, Velpatasvir, Ombitasvir, Elbasvir) or a non-nucleoside inhibitor of HCV polymerase (Dasabuvir) who fail to achieve SVR, select resistance associated substitutions (RASs) in the NS3, NS5A and polymerase region. RASs to protease inhibitors decrease progressively and become undetectable by mean of population sequencing within months until 2 years after treatment cessation, whereas RASs to NS5A inhibitors are fit and remain dominant for many years [53, 54].

GT-1 patients who failed after previous triple therapy with PEG-interferon, Ribavirin and a 1st generation protease inhibitor (Telaprevir, Boceprevir) or Simeprevir should be retreated with an IFN-free protease inhibitor-free regimen. A combination of Sofosbuvir, NS5A inhibitor (Ledipasvir, Velpatasvir or Daclatasvir) and RBV for 12 weeks is recommended [A1]. These recommendations are based on the results of ION-2 and ASTRAL-1 and ALLY-1 RCTs [31, 55, 56].

Patients who failed a previous Sofosbuvir-based regimen (Sofosbuvir alone, Sofosbuvir and RBV, Sofosbuvir plus RBV and PEG-IFN or Sofosbuvir plus Simeprevir – which considered now to be suboptimal) can be retreated with 1) Sofosbuvir/Velpatasvir (all genotypes), 2) Sofosbuvir/Ledipasvir (GT-1, 4, 5, 6), 3) ritonavir/Paritaprevir/Ombitasvir plus Dasabuvir (GT1), 4) ritonavir/Paritaprevir/Ombitasvir FDC (GT-4), 5) Grazoprevir/Elbasvir (GT-1, 4; 24 weeks if HCV RNA>800,000 IU/ml), 6) Sofosbuvir and Daclatasvir (all genotypes) for 12 weeks [B1].

Patients who failed a DAAs-containing regimen should be retreated with an IFN-free regimen, with weight based RBV for 12 weeks, if they have METAVIR F0-F2 fibrosis or for 24 weeks if they have F3-F4 fibrosis [B1].

GT-1 and 4 patients who failed on a regimen containing an NS5A inhibitor (Ledipasvir, Daclatasvir, Velpatasvir, Ombitasvir, Elbasvir) should be retreated with 1) Sofosbuvir plus ritonavir/Paritaprevir/Ombitasvir FDC and Dasabuvir (GT-1), 2) Sofosbuvir plus ritonavir/Paritaprevir/Ombitasvir FDC (GT-4), 3) Sofosbuvir plus Grazoprevir/Elbasvir FDC (GT-1, GT-4), 4) Sofosbuvir plus Daclatasvir plus Simeprevir for 12 weeks (GT-1b, GT-4, F0-2 METAVIR) or for 24 weeks (GT-1a, F3-F4 METAVIR) with weight-based RBV [B1].

GT-2, 3, 5, and 6 patients who failed on a regimen containing an NS5A inhibitor (Ledipasvir, Daclatasvir, Velpatasvir) should be retreated with the combination Sofosbuvir/Velpatasvir FDC for 24 weeks with weight-based RBV [B1].

Patients without an urgent need for retreatment can wait until alternative therapeutic options or more data become available [A1].

The utility of HCV resistance testing in patients who failed on any previous DAA-containing regimen is unclear. If reliable resistance testing is available, it can guide retreatment according to resistance profile and probability of SVR, in a multidisciplinary experienced team [B2].

CONCLUSIONS

This position paper represents a guide for the assessment and therapy of HCV infection. This completes the first part published in the previous issue of this journal. The recommendations are in concordance with other guidelines, but are applied to the real-life conditions of our country.

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