Treatment of Chronic Hepatitis C - August 2018 Update
SASL-SSI Expert Opinion Statement

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Introduction

This document represents an update of the last version of the Swiss Association for the Study of the Liver (SASL) and Swiss Society for Infectious Diseases (SSI) Expert Opinion Statement (EOS) on the Treatment of Chronic Hepatitis C published in November 2017 (www.sasl.ch; www.sggssg.ch, www.sginf.ch). Recommendations are based on the results of phase 3 or selected phase 2 clinical studies (1-10), the European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C (www.easl.eu) (11) and the Recommendations by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) (http://hcvguidelines.org). The reader is referred to these documents as well as the 'Fachinformation' approved by Swissmedic (www.compendium.ch or www.swissmedicinfo.ch) and the "Spezialitätenliste" of the Swiss Federal Office of Public Health (FOPH) (www.spezialitaetenliste.ch) for further information, including key references and sustained virologic response (SVR) rates that can be expected with the different treatment regimens as well as current reimbursement. The Swiss HCV Advisor App (www.hcvadvisor.com) is based on this EOS and has been endorsed by SASL and SSI. It provides rapid information on recommended treatment regimens.

The landscape of hepatitis C treatment has changed dramatically over the last years. At this point, it is unlikely that additional drugs for the treatment of hepatitis C will be licensed in the future. An exhaustive discussion of all aspects is beyond the scope of this EOS. Its aim is rather to provide practical and concise guidance.

Sofosbuvir alone (Sovaldi®), daclatasvir (Daklinza®), simeprevir (Olysio®), the ledipasvir/sofosbuvir fixed-dose combination (Harvoni®) as well as the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (Viekirax® and Exviera®) are no longer included in this update, as they have been largely replaced by newer direct acting antivirals (DAAs). Please consult the SASL-SSI EOS of November 2017 (available from the secretaries of SASL and SSI) for information on these drugs and drug combinations.

Treatment should be evaluated and can now be offered to all persons with HCV infection. However, reimbursement of DAAs is still limited to prescription by gastroenterologists, infectious diseases specialists and selected, named other specialists (www.bag.admin.ch/ls-ref).

Background

Hepatitis C virus (HCV) chronically infects 60-80 million individuals worldwide (12). A recent report commissioned by the FOPH estimates that 36,000-43,000 persons are chronically infected in Switzerland (13).

Recommendations for healthcare provider-initiated testing for HCV infection have been issued by the Swiss Experts in Viral Hepatitis (SEVHep) and the FOPH (14). Complementary screening modalities are being considered within the framework of the Swiss Hepatitis Strategy (www.hepatitis-schweiz.ch) (15).

The clinical course of chronic hepatitis C depends on a number of modifiable (alcohol, coinfections with hepatitis B virus [HBV] or human immunodeficiency virus [HIV], non-alcoholic fatty liver disease) and unmodifiable factors (age at the time of infection, sex, genotype 3, host genetics); 2-20% may develop cirrhosis over the first 20 years of infection, and disease progression may be accelerated in a non-linear fashion thereafter, with an estimated 15-30% developing cirrhosis after 30 years. Current efforts and goals set by the WHO and the Swiss Hepatitis Strategy aim to reduce the disease burden (decompensated liver cirrhosis hepatocellular carcinoma [HCC], liver transplantation [LT] and mortality), which in Switzerland has been projected to reach a peak only around 2030 if more efficient means of screening and treatment were not implemented (16, 17).

Pre-treatment assessment

Before starting antiviral treatment, other causes that contribute to the progression of liver disease should be carefully evaluated. All patients should be tested for markers of HBV (HBsAg, anti-HBc, anti-HBs) and HIV coinfection. Patients without previous hepatitis A virus or HBV exposure or vaccination should be vaccinated.

Hepatitis B reactivation has been observed in HBsAg-and/or anti-HBc-positive patients during or after antiviral treatment for HCV (18). Therefore, concurrent antiviral treatment with an HBV nucleos(t)ide analogue is recommended in HBsAg-positive patients. In patients with negative HBsAg but positive anti-HBc ± anti-HBs EASL recommends to monitor ALT and to test for HBsAg and HBV DNA in those in which ALT does not normalize or rises during or after antiviral therapy of chronic hepatitis C (11).

Alcohol consumption should be determined and quantified. Specific counseling to stop any harmful alcohol use should be provided. In addition, components of the metabolic syndrome (weight, BMI, diabetes mellitus, hyperlipidemia, arterial hypertension) should be determined and appropriate counseling and/or treatment initiated, as indicated. Other causes of chronic liver disease such as hemochromatosis should also be excluded.

As current treatment regimens are partially determined by the fibrosis stage and previous treatments, a detailed treatment history has to be obtained. The stage of fibrosis can be assessed with either a liver biopsy or transient elastography (FibroScan®). In patients with cirrhosis, determination of liver function (Child-Pugh score) and assessment of portal hypertension are essential. Protease inhibitor-based treatment regimens should only be considered in patients with well-compensated liver function (Child-Pugh A) and without history of prior decompensation.

Before deciding on the treatment regimen and treatment duration, it is important to determine the HCV genotype and serum HCV RNA load. If the viral genotype has not been determined recently, HCV genotyping should be repeated.

In order to gather real-life data on the natural history and outcomes of HCV infection in Switzerland, we encourage the inclusion of HCV-infected patients in the Swiss Hepatitis C Cohort Study (SCCS; www.swisshcv.org) or of HIV-coinfected patients in the Swiss HIV Cohort Study (SHCS; www.shcs.ch).

Practical use of the grazoprevir/elbasvir fixed-dose combination

Grazoprevir (GZR), a second-generation HCV NS3-4A protease inhibitor, and elbasvir (EBR), an NS5A inhibitor, are available in a fixed-dose combination of 100 mg GZR and 50 mg EBR (Zepatier®, Merck, Kenilworth, NJ). It is administered at a dose of one tablet per day with or without food.

GRZ/EBR shows activity against HCV genotypes 1 as well as 4 and is approved and reimbursed in Switzerland for the treatment of these two genotypes. It is listed only for patients with HCV genotype 1b infection in the updated recommended treatment options (Table 1) but may still be considered also for treatment-naïve patients with HCV genotype 4 infection and a baseline HCV RNA < 8 x 10^5 IU/ml.

GZR/EBR is generally well tolerated; the most commonly reported adverse effects are fatigue and headache. Liver enzymes should be measured before treatment initiation and at week 8 during treatment because in 1% of the study patients an elevation has been observed. For drug-drug interactions and contraindicated co-medications, please consult www.hep-druginteractions.org or other sources.

Dose modification in patients with renal impairment is not necessary. GZR/EBR can therefore be used in patients with advanced renal impairment (19). GZR/EBR is contraindicated in case of significant liver impairment (Child-Pugh B and C) or in patients with a history of decompensation.

In patients with HCV genotype 1a baseline resistance testing has to be performed to identify potential NS5A polymorphisms (M28T/A, Q30E/H/R/G/K/L/D, L31M/V/F and Y93C/H/N) as these significantly reduce rates of SVR12 with a 12-week course of GZR/EBR. If such a polymorphism has been detected the total GZR/EBR treatment duration is 16 weeks in combination with weight-based ribavirin (RBV; 1000 mg [< 75 kg] to 1200 mg [≥ 75 kg] per day in two doses). Resistance testing is reimbursed by the manufacturer of GZR/EBR. Prolongation of GZR/EBR treatment to 16 weeks in combination with RBV is also indicated for patients with genotype 4 infection who failed a previous treatment with PEG-IFN-α and RBV (relapse excluded). However, the 16-week regimens comprising RBV are no longer recommended in light of the currently available alternatives.

Practical use of the velpatasvir/sofosbuvir fixed-dose combination

Velpatasvir (VEL) is an NS5A inhibitor and sofosbuvir (SOF) a nucleotidic polymerase inhibitor, both with pangenotypic activity. They are administered once daily with or without food in a fixed-dose combination single pill containing 100 mg of VEL and 400 mg of SOF (Epclusa®, Gilead Sciences, Foster City, CA).

VEL/SOF is generally well tolerated; the most commonly reported adverse effects include headache, fatigue and nausea. For drug-drug interactions and contraindicated co-medications, please consult www.hep-druginteractions.org or other sources. The combination of SOF and another DAA with amiodarone has been linked to instances of severe bradycardia and is therefore contraindicated. Due to the long half-life of amiodarone, interaction with SOF is possible for several months after discontinuation of amiodarone. Therefore, it is recommended to wait for at least 3 months after discontinuation of amiodarone before starting a SOF-containing regimen. If considered necessary, a proton pump inhibitor (PPI) at a maximum dose equivalent to 20 mg omeprazole may be taken 4 hours after VEL/SOF. Similarly, H2 receptor antagonists may be administered simultaneously with or 12 hours apart from VEL/SOF at a dose that does not exceed doses comparable to famotidine 20 mg twice daily.

SOF and its main metabolite GS-331007 are eliminated predominantly by the kidney. Therefore, VEL/SOF is not recommended in patients with severe renal impairment (GFR < 30 ml/min). VEL/SOF has been studied in patients with decompensated cirrhosis (5) and was generally well tolerated in this setting. Therapeutic drug monitoring for SOF and GS-331007 is available at the Division of Clinical Pharmacology of the CHUV (www.chuv.ch/pcl).

Safety and efficacy of VEL/SOF were assessed in the phase III Astral studies as well as in Polaris studies 2 and 3 (3-5, 10). This combination therapy achieved cure rates > 95% across all genotypes. Suboptimal SVR rates were only observed in genotype 3-infected cirrhotic or treatment-experienced patients with pre-existing NS5A RASs (particularly the Y93H substitution). Accordingly, the presence of this variant should be excluded or RBV added in this situation (Table 1).

Practical use of the voxilaprevir/velpatasvir/sofosbuvir fixed-dose combination

Voxilaprevir (VOX), a second-generation HCV NS3-4A protease inhibitor, is administered once daily with food in a fixed-dose combination single pill containing 100 mg of VOX, 100 mg of VEL and 400

mg of SOF (Vosevi®, Gilead Sciences, Foster City, CA). The combination has pangenotypic activity. It is approved by Swissmedic for patients who failed an NS5A inhibitor-containing regimen but it is not reimbursed yet. Hence, reimbursement has to be requested under article 71 (https://www.vertrauensaerzte.ch/tools/dynaforms_kvv71/).

VOX/VEL/SOF is generally well tolerated. The most commonly reported adverse effects include headache, diarrhea and nausea; gastrointestinal side effects are more common than with VEL/SOF alone. For drug-drug interactions and contraindicated co-medications, please consult www.hep-druginteractions.org or other sources. Concomitant treatment with amiodarone is contraindicated (see above). If considered necessary, a PPI at a maximum dose equivalent to 20 mg omeprazole may be taken 4 hours after VOX/VEL/SOF.

VOX/VEL/SOF is not recommended in patients with severe renal impairment (GFR < 30 ml/min; see above). VOX/VEL/SOF is contraindicated in case of significant liver impairment (Child-Pugh B and C) or in patients with a history of decompensation.

VOX/VEL/SOF is recommended as salvage therapy in patients who do not achieve an SVR after a DAA-based regimen other than SOF combined with PEG-IFN-α and RBV or SOF combined with RBV. It is given for 12 weeks without RBV in patients with genotype 1-6 infection without or with compensated cirrhosis. The adjunction of RBV may be considered in very difficult-to-cure patients such as cirrhotic patients with resistance to two DAA classes or in cirrhotic patients with genotype 3 infection and resistance to NS5A inhibitors (http://hcvguidelines.org) (11). However, this is not supported by study data.

Practical use of the glecaprevir/pibrentasvir fixed-dose combination

Glecaprevir (GLE), a second-generation HCV NS3-4A protease inhibitor, and pibrentasvir (PIB), a second-generation NS5A inhibitor, are available in a fixed-dose combination of 100 mg GLE and 40 mg PIB (Maviret®, AbbVie, North Chicago, IL). The combination has pangenotypic activity. It is administered once daily at a dose of three tablets with food. GLE/PIB shows pangenotypic activity.

GLE/PIB is generally well tolerated; the most commonly reported adverse effects include headache and fatigue. For drug-drug interactions and contraindicated co-medications, please consult www.hep-druginteractions.org or other sources.

Dose modification in patients with renal impairment is not necessary. GLE/PIB can therefore be used in patients with advanced renal impairment (20). GLE/PIB is contraindicated in case of significant liver impairment (Child-Pugh B and C) or in patients with a history of decompensation.

HCV RNA monitoring on treatment

It is recommended to determine HCV RNA at baseline, week 2 or 4 (assessment of adherence, optional), week 12 or 24 (end of treatment, optional), at 12 weeks after the end of treatment (SVR12) and 3-9 months later (i.e. 6 to 12 months after the end of treatment, optional).

Follow-up after SVR

If HCV RNA is negative 6 to 12 months after the end of treatment, patients can be considered as definitively cured. HCV RNA determination is no longer necessary, unless the patient has an ongoing or new risk behavior for HCV reinfection (illicit drug use, high-risk sexual practices).

Patients with an indication for HCC surveillance as recommended by international guidelines should continue to have 6-monthly abdominal ultrasound and - depending on local custom - alpha-fetoprotein measurement. EASL recommends HCC surveillance for all patients with Metavir stage ≥ F3 or FibroScan > 9.5 kPa, other guidelines (e.g. EACS) recommend HCC surveillance for cirrhotic patients only. FibroScan > 12.5 kPa is considered to indicate cirrhosis. Patients with cirrhosis should undergo screening for esophageal varices as recommended in the Baveno VI consensus statement (21). According to this statement, patients with compensated cirrhosis can safely avoid endoscopy in case of a platelet count > 150 G/L and a FibroScan < 20 kPa. Patients without advanced liver disease (F0-

F2; FibroScan ≤ 9.5 kPa) but with cofactors for liver disease progression (alcohol use, metabolic syndrome, non-alcoholic fatty liver disease etc.) should be periodically (once a year) assessed for liver disease progression. Patients without significant liver fibrosis (Metavir F0-F1; FibroScan < 7.5 kPa) and without risk factors for disease progression can be released from specialized care.

Special patient populations

Response rates to DAAs are similar in HCV-HIV-coinfected as compared to HCV-monoinfected patients. Therefore, treatment indications and regimens for HCV-HIV-coinfected patients should in general follow those of HCV-monoinfected patients. Specific recommendations for the management of HCV infection in HIV-infected patients are updated regularly by the European AIDS Clinical Society (www.eacsociety.org). Because of the frequent co-medication with antiretrovirals and other drugs, it is crucial to check for drug-drug interactions (www.hep-druginteractions.org) before starting DAA treatments. However, in the large majority of patients, drug-drug interactions are manageable and should not be a barrier to starting DAA therapy.

Ledipasvir/sofosbuvir (LDV/SOF) may still be used in treatment-naïve patients with HCV genotype 1 infection, Metavir fibrosis stage ≤ F2 and HCV RNA < 6 x 10^6 (6.8 log) IU/ml who desire an 8-week treatment or in rare cases for HIV-coinfected individuals on an etravirine-, efavirenz- or nevirapine-based antiretroviral regimen with no other option.

Expert advice should be sought for adolescents as well as patients with DAA failure, decompensated cirrhosis, HCC, renal insufficiency, pre- or post-LT, other organ transplant recipients and acute hepatitis C.

Patients with decompensated cirrhosis

Antiviral treatment of patients with decompensated liver disease (Child-Pugh B and C) should be pursued in close collaboration with an experienced center. These patients should be evaluated for LT. Protease inhibitor-based regimens are contraindicated in patients with Child-Pugh B and C cirrhosis. They can be treated with LDV/SOF (genotype 1) or VEL/SOF (all genotypes) in combination with weight-based RBV (1000 mg or 1200 mg per day in patients < 75 or ≥ 75kg, respectively) (5, 22, 23). The combination of LDV/SOF with RBV is not foreseen in the Swiss label and not reimbursed. RBV can be started at a dose of 600 mg and increased to the recommended dose as tolerated. If RBV is contraindicated or not tolerated, treatment should be prolonged to 24 weeks, but this is not foreseen for VEL/SOF in the Swiss label and is not reimbursed. As adverse events are more frequent in patients with decompensated liver disease, close monitoring is mandatory. In patients on the LT waiting list and with a MELD score > 18-20, treatment might be deferred until after LT, depending on the estimated waiting time

Retreatment of patients with DAA failure

Resistance testing is recommended in patients who do not achieve an SVR after a DAA-based regimen other than SOF combined with PEG-IFN-α and RBV or SOF combined with RBV. Reimbursement for resistance testing should be clarified beforehand.

VOX/VEL/SOF for 12 weeks is recommended as salvage therapy in patients who do not achieve an SVR after a DAA-based regimen other than SOF combined with PEG-IFN-α and RBV or SOF combined with RBV. It is approved by Swissmedic but not reimbursed yet for this indication (see above). VOX/VEL/SOF is contraindicated in case of significant liver impairment (Child-Pugh B and C) or in patients with a history of decompensation. The adjunction of RBV may be considered in very difficult-to-cure patients such as cirrhotic patients with resistance to two DAA classes or in cirrhotic patients with genotype 3 infection and resistance to NS5A inhibitors (http://hcvguidelines.org) (11). However, this is not supported by study data.

The combination of GLE/PIB and SOF represents an alternative to VOX/VEL/SOF. However, this combination is not approved and the same restrictions apply in patients with decompensated cirrhosis (Child-Pugh B and C).

Recommended treatment options for patients with chronic hepatitis C

Recommended treatment options are summarized in Table 1.

Table 1. Recommended treatment options for patients with chronic hepatitis C.

A. Treatment-naïve patients

Genotype	Non-cirrhotic	Cirrhotic (Child-Pugh A)
1a	VEL/SOF for 12 wks GLE/PIB for 8 wks	VEL/SOF for 12 wks GLE/PIB for 12 wks
1b	GZR/EBR for 12 wks[1] VEL/SOF for 12 wks GLE/PIB for 8 wks	GZR/EBR for 12 wks VEL/SOF for 12 wks GLE/PIB for 12 wks
2	VEL/SOF for 12 wks GLE/PIB for 8 wks	VEL/SOF for 12 wks GLE/PIB for 12 wks
3	VEL/SOF for 12 wks GLE/PIB for 8 wks	VEL/SOF ± RBV for 12(-24) wks[2] GLE/PIB for 12 wks VOX/VEL/SOF for 12 wks
4	VEL/SOF for 12 wks GLE/PIB for 8 wks	VEL/SOF for 12 wks GLE/PIB for 12 wks
5 and 6	VEL/SOF for 12 wks GLE/PIB for 8 wks	VEL/SOF for 12 wks GLE/PIB for 12 wks

Color code: **green** = approved and reimbursed (please consult www.spezialitaetenliste.ch for eventual updates); **blue** = according to the current Swiss label, but with potential modifications of treatment duration and/or the addition of RBV; **bordeaux** = off-label use of a drug approved but not reimbursed yet in Switzerland.

[1] Treatment-naïve patients with Metavir fibrosis stage ≤ F2 may be treated for 8 weeks.

[2] Patients with cirrhosis should be treated with VEL/SOF + RBV for 12 weeks or with VEL/SOF for 24 wks if RBV-intolerant. Extension to 24 weeks in patients who cannot tolerate RBV requires approval by health insurances. If NS5A resistance testing is performed and demonstrates the absence of NS5A RAS Y93H, treatment can be performed with VEL/SOF for 12 weeks without RBV.

B. Treatment-experienced patients (defined as patients who were previously treated with PEG-IFN-α and RBV; SOF, PEG-IFN-α and RBV; or SOF and RBV)

Genotype	Non-cirrhotic	Cirrhotic (Child-Pugh A)
1a	**VEL/SOF for 12 wks** **GLE/PIB for 8 wks**	**VEL/SOF for 12 wks** **GLE/PIB for 12 wks**
1b	**GZR/EBR for 12 wks** **VEL/SOF for 12 wks** **GLE/PIB for 8 wks**	**GZR/EBR for 12 wks** **VEL/SOF for 12 wks** **GLE/PIB for 12 wks**
2	**VEL/SOF for 12 wks** **GLE/PIB for 8 wks**	**VEL/SOF for 12 wks** **GLE/PIB for 12 wks**
3	**VEL/SOF ± RBV for 12(-24) wks**[3] **GLE/PIB for 16 wks**	**VEL/SOF ± RBV for 12(-24) wks**[4] **GLE/PIB for 16 wks** **VOX/VEL/SOF for 12 wks**
4	**VEL/SOF for 12 wks** **GLE/PIB for 8 wks**	**VEL/SOF for 12 wks** **GLE/PIB for 12 wks**
5 and 6	**VEL/SOF for 12 wks** **GLE/PIB for 8 wks**	**VEL/SOF for 12 wks** **GLE/PIB for 12 wks**

Color code: **green** = approved and reimbursed (please consult www.spezialitaetenliste.ch for eventual updates); **blue** = according to the current Swiss label, but with potential modifications of treatment duration and/or the addition of RBV; **bordeaux** = off-label use of a drug approved but not reimbursed yet in Switzerland.

[3] The use of RBV in treatment experienced patients without cirrhosis is discussed controversially. EASL recommends VEL/SOF for 12 weeks while AASLD recommends VEL/SOF for 12 weeks in the absence of NS5A RAS Y93H and VEL/SOF + RBV for 12 weeks in the presence of NS5A RAS Y93H. VEL/SOF for 24 wks may be considered in the latter case if RBV-intolerant. Extension to 24 weeks in patients who cannot tolerate RBV requires approval by health insurances.

[4] Treatment experienced patients with cirrhosis should be treated with VEL/SOF + RBV for 12 weeks or with VEL/SOF for 24 wks if RBV-intolerant. Extension to 24 weeks in patients who cannot tolerate RBV requires approval by health insurances. If NS5A resistance testing is performed and demonstrates the absence of NS5A RAS Y93H, treatment can be performed with VEL/SOF for 12 weeks without RBV.

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