Treatment of Chronic Hepatitis C - January 2021 Update
Expert Opinion Statement by SASL, SSG and SSI

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Introduction

This document represents an update of the Expert Opinion Statement (EOS) on the Treatment of Chronic Hepatitis C by the Swiss Association for the Study of the Liver (SASL), the Swiss Society of Gastroenterology (SSG) and the Swiss Society for Infectious Diseases (SSI) (www.sasl.ch; www.sggssg.ch; www.sginf.ch). The first EOS of this series was published by SASL in 2012 (1). Subsequent updates, the last one dating of August 2018, were prepared jointly by SASL and SSI and published online.

Recommendations are based on the results of phase 3 or selected phase 2 clinical studies (2-13), the European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C (14) (www.easl.eu) and the Hepatitis C Virus (HCV) Guidance by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) (15) (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 (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 application (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 significantly over the last years. At this point, it is unlikely that directly acting antivirals (DAAs) other to the ones listed in Table 1 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 DAAs.

Treatment should be evaluated and 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).

Table 1. Currently recommended DAAs against hepatitis C.

Class	Generic name	Abbrev.	Fixed-dose combinations
Protease inhibitors	Grazoprevir Glecaprevir Voxilaprevir	GZR GLE VOX	**Zepatier®** GZR EBR **Epclusa®** VEL SOF **Vosevi®** VOX VEL SOF **Maviret®** GLE PIB
NS5A inhibitors	Elbasvir Velpatasvir Pibrentasvir	EBR VEL PIB	
Polymerase inhib.	Sofosbuvir	SOF	

Background

Hepatitis C virus (HCV) chronically infects an estimated 71 million individuals worldwide (16) and 36,000-43,000 in Switzerland (17), many of whom are still unaware of their infection.

Recommendations for healthcare provider-initiated testing for HCV infection have been issued by the Swiss Experts in Viral Hepatitis (SEVHep) and the FOPH (18). Complementary screening modalities are being considered within the framework of the Swiss Hepatitis Strategy (www.hepatitis-schweiz.ch). The impact of the ongoing COVID-19 pandemic on global HCV elimination efforts is currently difficult to appraise but may be considerable (19).

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], metabolic dysfunction-associated fatty liver disease) and unmodifiable factors (age at the time of infection, gender, 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 goals set by the WHO aim to eliminate, i.e. to control chronic hepatitis C by 2030 and to thereby reduce the associated disease burden (decompensated liver cirrhosis hepatocellular carcinoma [HCC], liver transplantation [LT] and mortality) (20).

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 (21). Therefore, concurrent antiviral treatment with an HBV nucleos(t)ide analogue is recommended in HBsAg-positive patients for at least 12 weeks after the end of antiviral therapy of chronic hepatitis C, with monthly monitoring once HBV treatment is stopped. 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 (14).

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.

For drug-drug interactions and contraindicated co-medications, please consult www.hep-druginteractions.org, the Liverpool HEP iChart application or other sources.

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 by non-invasive methods such as vibration-controlled transient elastography (VCTE, FibroScan®) or acoustic radiation force impulse (ARFI). 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, we recommend to determine the HCV genotype and serum HCV RNA load. If the viral genotype has not been determined recently, HCV genotyping should be repeated. Subtyping and sequencing of the NS5A region are recommended in migrants from certain regions in Africa and Asia where distinct subtypes with limited response to current regimens are prevalent, especially genotypes 1 non-1a/1b (particularly 1l), 3 non-3a (particularly 3b and 3g) as well as 4 non-4a/4d (particularly 4r), and may require tailored antiviral therapy.

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 antiviral regimens

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. However, it is recommended only for patients with HCV genotype 1b infection in this updated EOS.

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 study patients an elevation has been observed. For drug-drug interactions and contraindicated co-medications, please consult www.hep-druginteractions.org, the Liverpool HEP iChart application 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 (22). GZR/EBR is contraindicated in case of significant liver impairment (Child-Pugh B and C) or in patients with a history of decompensation.

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, the Liverpool HEP iChart application 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.

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 (6) and was generally well tolerated in this setting. Therapeutic drug monitoring for SOF and GS-331007 is available at the Service 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 (4-6, 13). 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 resistance-associated substitutions (RAS) in NS5A (particularly the Y93H substitution). Accordingly, the presence of this variant should be excluded or RBV added in this situation (Table 2).

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 is still not reimbursed. 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, the Liverpool HEP iChart application 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 cirrhosis or with compensated cirrhosis. The adjunction of RBV may be considered in very difficult-to-cure patients such as patients with cirrhosis and resistance to two DAA classes or patients with cirrhosis and genotype 3 infection with resistance to NS5A inhibitors (14, 15).

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 is generally well tolerated; the most commonly reported adverse effects include headache and fatigue. The combination with ethinylestradiol-containing contraception is contraindicated. For other drug-drug interactions and contraindicated co-medications, please consult www.hep-druginteractions.org, the Liverpool HEP iChart application 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 (23). GLE/PIB is contraindicated in case of significant liver impairment (Child-Pugh B and C) or in patients with a history of decompensation.

Recommended treatment options for patients with chronic hepatitis C

Recommended treatment options are summarized in Table 2. Expert advice should be sought for subtypes 1l, 3b and 3g as well as 4r and other subtypes naturally harboring one or more NS5A RAS.

Table 2A. Treatment options for treatment-naïve patients with chronic hepatitis C.

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 8 wks[2]
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 8 wks[2]
2	VEL/SOF for 12 wks GLE/PIB for 8 wks	VEL/SOF for 12 wks GLE/PIB for 8 wks[2]
3	VEL/SOF for 12 wks GLE/PIB for 8 wks	VEL/SOF ± RBV for 12(-24) wks[3] GLE/PIB for 8 wks[2] VOX/VEL/SOF for 12 wks[3]
4	VEL/SOF for 12 wks GLE/PIB for 8 wks	VEL/SOF for 12 wks GLE/PIB for 8 wks[2]
5 and 6	VEL/SOF for 12 wks GLE/PIB for 8 wks	VEL/SOF for 12 wks GLE/PIB for 8 wks[2]

See Table 1 for abbreviations. RBV, ribavirin; wks, weeks.

[1] Treatment-naïve patients with Metavir fibrosis stage ≤ 2 may be treated for 8 weeks.

[2] Treatment duration may be extended to 12 weeks depending on factors such as the presence of genotype 3, portal hypertension or coinfection with HIV. However, extension to 12 weeks requires approval by health insurances.

[3] If resistance testing is performed, patients with the NS5A RAS Y93H at baseline should be treated with VEL/SOF plus RBV for 12 weeks, with VOX/VEL/SOF for 12 weeks or with VEL/SOF alone for 24 weeks, whereas patients without the NS5A RAS Y93H should be treated with VEL/SOF alone for 12 weeks. Coverage by health insurance has to be solicited for VOX/VEL/SOF or for the extension of VEL/SOF to 24 weeks.

Table 2B. Treatment options for treatment-experienced patients[1] with chronic hepatitis C.

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[2] GLE/PIB for 16 wks	VEL/SOF ± RBV for 12(-24) wks[3] GLE/PIB for 16 wks VOX/VEL/SOF for 12 wks[3]
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

See Table 1 for abbreviations. RBV, ribavirin; wks, weeks.

[1] Treatment-experienced patients are defined as patients who were previously treated with PEG-IFN-α and ribavirin, PEG-IFN-α, ribavirin and SOF, or SOF and RBV.

[2] 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 or another regimen in the presence of NS5A RAS Y93H. VEL/SOF for 24 weeks may be considered in the latter case if RBV-intolerant. Extension to 24 weeks in patients who do not tolerate RBV requires approval by health insurances.

[3] If resistance testing is performed, patients with the NS5A RAS Y93H at baseline should be treated with VEL/SOF plus RBV for 12 weeks, with VOX/VEL/SOF for 12 weeks or with VEL/SOF alone for 24 weeks, whereas patients without the NS5A RAS Y93H should be treated with VEL/SOF alone for 12 weeks. Coverage by health insurance has to be solicited for VOX/VEL/SOF or for the extension of VEL/SOF to 24 weeks.

HCV RNA monitoring on treatment

It is recommended to determine HCV RNA at baseline, week 2 or 4 (assessment of adherence, optional), week 8 or 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 3 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) (Hepatitis Schweiz-SASL-SGG-SGInf-SHCV. Empfehlungen für die Nachsorge von Patienten mit ausgeheilter Hepatitis C. Submitted).

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 VCTE ≥ 10 kPa. Other guidelines (e.g. European AIDS Clinical Society, EACS) recommend HCC surveillance for all cirrhotic patients (VCTE ≥ 13 kPa) and surveillance based on an individual risk assessment for those with Metavir stage 3. Patients with cirrhosis should undergo screening for esophageal varices as recommended in the Baveno VI consensus statement (24). According to this statement, patients with compensated cirrhosis can safely avoid endoscopy in case of a platelet count > 150 G/L and a VCTE < 20 kPa. Patients without advanced liver disease (F0-F2; VCTE < 10 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; VCTE < 7.5 kPa) and without risk factors for disease progression can be discharged from specialized care.

Special patient populations

HCV-HIV coinfection

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 EACS (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 or the Liverpool HEP iChart application) 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, Harvoni®) 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.

Patients with decompensated cirrhosis

Expert advice should be sought for the management of 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 VEL/SOF in combination with weight-based RBV (1000 mg or 1200 mg per day in patients < 75 or ≥ 75kg, respectively) (6). RBV can be started at a dose of 600 mg per day 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 in the Swiss label and requires approval by the health insurance. 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

Expert advice should be sought for the management 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 still not reimbursed 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 (14, 15).

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).

Others

Expert advice should be sought for patients infected with subtypes 1l, 3b and 3g as well as 4r and other subtypes naturally harbouring one or more NS5A RAS, patients with HCC, organ transplant recipients and acute/recently acquired/early chronic hepatitis C. Data on DAA-based treatment of chronic hepatitis C in adolescents and children is emerging; please consult the EASL Recommendations on Treatment of Hepatitis C (14) (www.easl.eu) and the Hepatitis C Virus (HCV) Guidance by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) (15) (http://hcvguidelines.org) and liaise with an expert for these patients. With regard to the management of recently acquired hepatitis C among men who have sex with men, we refer to the European Treatment Network for HIV, Hepatitis and Global Infectious Diseases (NEAT-ID) Consensus statement (25). With regard to people who use drugs, we refer to the Swiss Federal Office of Public Health guidance available at https://www.bag.admin.ch/hepatitis-c.

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