



Treatment of Chronic Hepatitis C - September 2014 Update

Swiss Association for the Study of the Liver and Swiss Society for Infectious Diseases

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Introduction

The present document represents an update of the Swiss Association for the Study of the Liver (SASL) Expert Opinion Statement on the treatment of chronic hepatitis C with triple therapy comprising telaprevir (TVR¹) or boceprevir (BOC) (1). It has been elaborated by SASL jointly with the Swiss Society for Infectious Diseases (SSI) to also cover hepatitis C virus (HCV)-human immunodeficiency virus (HIV) coinfection. Recommendations are based on the results of phase 3 or selected phase 2 clinical studies (2-7) as well as the Clinical Practice Guidelines by the European Association for the Study of the Liver (EASL) (<http://www.easl.eu/clinical-practice-guideline>) (8), the Practice Guidelines by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) (<http://hcvguidelines.org>), as well as the recommendations by the Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS) (<http://www.dgvs.de/leitlinien/aktuelle-empfehlungen/aktuelle-empfehlung-der-dgvs-zur-therapie-der-chronischen-hepatitis-c/>). The reader is referred to these documents as well as the 'Fachinformation' on sofosbuvir (SOF) approved by Swissmedic in March 2014 (www.compendium.ch or www.swissmedicinfo.ch) for further information, including sustained virological response (SVR) rates that can be expected with the different treatment regimens.

Given the current very rapid progress in the treatment of chronic hepatitis C and the expected approval of several new antiviral drugs and treatment regimens within the next months, SASL and SSI have decided to post this and future updated Expert Opinion Statements on their websites rather than publishing them in print.

The present update takes into consideration the recent approval of SOF in Switzerland. It is important to note, however, that a number of additional directly acting antivirals (DAAs) are expected to be approved in 2014-2015, including simeprevir (SMV) (9-12), daclatasvir (DCV) (13, 14), the combination of ritonavir-boosted paritaprevir (paritaprevir/r), ombitasvir and dasabuvir (15-18), as well as a SOF-ledipasvir (LDV) fixed-dose combination (19-21). Recommendations will be updated as new drugs are being approved in Switzerland.

¹Abbreviations: TVR, telaprevir; BOC, boceprevir; DAA, directly acting antiviral; DCV, daclatasvir; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; LDV, ledipasvir; LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease; PEG-IFN- α , pegylated interferon- α ; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; TE, treatment-experienced; TN, treatment-naïve.

With these advances, robust interferon (IFN)-free combination therapies with short treatment duration (8 to 12 to 24 weeks) will become available for all genotypes. On this background, the decision to treat a patient with chronic hepatitis C today should take into account the urgency of antiviral treatment and patient wish on the one hand and chances of success, tolerability and availability of a given treatment regime on the other.

HCV chronically infects 120-200 million individuals worldwide and an estimated 80,000 (i.e. around 1% of the general population) in Switzerland (22). It is believed that about 50% of the latter have not been diagnosed yet. Recommendations for healthcare provider-initiated testing for HCV infection have been issued recently (23), and complementary birth cohort-based screening is being discussed (24). The Swiss Experts in Viral Hepatitis (SEVHep) have initiated to coordinate efforts to develop a national strategy for hepatitis C (www.viralhepatitis.ch).

The clinical course of chronic hepatitis C depends on a number of modifiable (alcohol, coinfections with hepatitis B virus [HBV] or HIV, nonalcoholic fatty liver disease [NAFLD]) 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. It is expected that the peak of the disease burden (decompensated liver cirrhosis, hepatocellular carcinoma [HCC], liver transplantation [LT] and mortality) will be reached in Switzerland only around 2030, unless more efficient means of screening and treatment for those in need of therapy are implemented (25, 26).

Practical use of sofosbuvir

Sofosbuvir (SOF; Sovaldi[®], Gilead Sciences, Foster City, CA, USA) is a uridine nucleotide inhibitor of the HCV NS5B RNA-dependent RNA polymerase, with potent pangenotypic activity and a high barrier to resistance. It is administered at a dose of one 400-mg tablet per day, with or without food. It has been approved in Switzerland in March 2014 and it is reimbursed, with certain limitations (see below), since August 2014.

SOF is generally well tolerated over 12 to 24 weeks of administration. The most commonly reported adverse effects are headache, fatigue and nausea.

The risk of drug-drug interactions, notably with most antirejection and antiretroviral treatments, is low. However, coadministration of potent P-glycoprotein inducers, such as rifampicin, carbamazepine, phenytoin or St. John's wort should be avoided, as they significantly decrease the plasma concentration of SOF.

SOF and its main metabolite GS-331007 are eliminated predominantly by the kidney. Therefore, SOF should not be administered to patients with severe renal impairment (estimated glomerular filtration rate < 30 ml/min/1.73 m²) or with end-stage renal disease until more data is available. SOF exposure is not significantly changed in patients with mild liver function impairment, but it is increased about 2- to 2.5-fold in those with moderate to severe hepatic impairment. However, dose adaptations are not recommended in this situation. Therapeutic drug monitoring for SOF is available at the Division of Clinical Pharmacology of the CHUV (www.chuv.ch/pcl).

Reimbursement in Switzerland of SOF in combination with ribavirin or pegylated interferon- α (PEG-IFN- α) and ribavirin (RBV) is currently limited to prescription by gastroenterologists, infectious diseases specialists, and selected, named addiction medicine and other specialists

(www.bag.admin.ch/lis-ref). Moreover, reimbursement is currently limited to patients with advanced fibrosis or cirrhosis (Metavir stage 3 and 4 or liver stiffness > 9.5 kPa, as determined by FibroScan® on two occasions ≥ 3 months apart), to patients with symptomatic extrahepatic manifestations of HCV infection, and to patients with chronic hepatitis C awaiting LT. For all other indications, reimbursement has to be negotiated with health insurances on an individual basis.

Currently recommended treatment schedules are listed in Table 1. Conventional combination therapy with PEG-IFN- α and RBV may still be considered in patients with a strong desire to be treated now, who are not included in current reimbursement limitations for SOF and who have good chances of achieving SVR with 24 weeks of conventional treatment (e.g., patients with genotype 1 infection, low viral load, Metavir fibrosis stage F2 and a rapid virologic response or patients with genotype 2 infection and Metavir fibrosis stage F2).

Treatment of hepatitis C in HIV-coinfected patients

HCV infection is a leading cause of morbidity and mortality in HIV-infected patients (27). Unfortunately, HCV treatment uptake has been limited so far due to multiple barriers to therapy (28). In the Swiss HIV Cohort Study (SHCS), only about 30% of patients received therapy because of fear of adverse effects as well as reluctance of patients and physicians to start IFN-based therapy². Treatment uptake remained low after the introduction of TVR and BOC. However, the newer DAA-based therapies offer unprecedented opportunities for treating HCV infection by increasing considerably treatment efficacy and tolerability. Importantly, 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. No significant drug-drug interactions with antiretroviral drugs are expected for SOF, with the exception of nelfinavir and tipranavir which are rarely used in clinical practice. The drug interactions database from the University of Liverpool (www.hep-druginteractions.org) offers a highly valuable tool if other DAAs are considered in clinical practice.

The currently recommended treatment schedules listed in Table 1 also apply to HCV-HIV coinfected patients. Combinations of SOF with DCV or SMV can also be considered in HIV infected patients within the framework of early access programs. However, access to DCV and SMV is currently limited to selected patients with advanced liver disease or with extrahepatic manifestations of HCV infection. Furthermore, DCV and particularly SMV cause significant drug-drug interactions with antiretroviral treatments. SOF + RBV for 24 weeks may be considered in IFN-ineligible patients with HCV genotype 1, 3 or 4 infection who cannot be treated with SOF + DCV or with SOF + SMV and in whom treatment cannot be deferred until the approval of new DAAs in Switzerland (see Table 1) (6). An update of the guidelines of the European AIDS Clinical Society will be published late 2014 (www.eacsociety.org). In addition, the AASLD-IDSA guidance includes specific recommendations for HCV-HIV coinfected patients (<http://hcvguidelines.org>).

²Kovari H *et al.* Joint Annual Meeting of the SSI, SSHH and SSTTM. Aarau, August 28-29, 2014.

Table 1. Currently recommended treatment schedules for chronic hepatitis C.

Genotype	Treatment-naïve	Treatment-experienced
1	SOF + PEG-IFN- α + RBV for 12 wks IFN-ineligible: seek expert advice ¹	Seek expert advice ²
2	SOF + RBV for 12 wks ³ Alternative: SOF + PEG-IFN- α + RBV for 12 wks (cirrhotic and/or TE)	SOF + RBV for 12 wks ³ Alternative: SOF + PEG-IFN- α + RBV for 12 wks (cirrhotic and/or TE)
3	SOF + PEG-IFN- α + RBV for 12 wks Alternative: SOF + RBV for 24 wks ⁴	Seek expert advice ²
4	SOF + PEG-IFN- α + RBV for 12 wks IFN-ineligible: seek expert advice ⁵	Seek expert advice ²
5-6	SOF + PEG-IFN- α + RBV for 12 wks	Seek expert advice ²

Abbreviations: IFN, interferon; PEG-IFN- α , pegylated interferon- α ; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; wks, weeks.

SOF is administered at a dose of 400 mg per day. PEG-IFN- α is administered at a dose of 180 μ g per week for PEG-IFN- α 2a or 1.5 μ g per kg per week for PEG-IFN- α 2b. RBV is administered at a dose of 1000 mg (< 75 kg) or 1200 mg (\geq 75 kg) per day.

¹SOF + RBV for 24 wks is recommended only if no other IFN-free option is available, as SVR rates are unsatisfactory. SOF + SMV \pm RBV, SOF + DCV \pm RBV, SOF-LDV or the combination of paritaprevir/r, ombitasvir and dasabuvir \pm RBV may be considered within the framework of early access programs or authorization by Swissmedic as well as reimbursement by health insurances if applicable. For patients with HCV genotype 1a infection, pretreatment testing for the NS3 Q80K variant is recommended (see below) but not mandatory if SMV is to be used together with SOF \pm RBV.

²Given the current limited data, it is recommended to seek expert advice before initiating retreatment of TE patients. SOF + PEG-IFN- α + RBV may be considered in IFN-eligible patients. Alternatively, SOF + SMV \pm RBV, SOF + DCV \pm RBV, SOF-LDV or the combination of paritaprevir/r, ombitasvir and dasabuvir \pm RBV may be considered for patients with HCV genotype 1 infection within the framework of early access programs or authorization by Swissmedic as well as reimbursement by health insurances if applicable. For patients with HCV genotype 1a infection, pretreatment testing for the NS3 Q80K variant is recommended (see below) but not mandatory if SMV is to be used together with SOF \pm RBV. For TE patients with genotype 3 infection, SOF + PEG-IFN- α + RBV or SOF + DCV \pm RBV represent valuable options. Alternatively, SOF + RBV for 24 wks may be considered. For TE patients with genotype 4 infection, SOF + PEG-IFN- α + RBV, SOF + SMV \pm RBV or SOF + DCV \pm RBV represent valuable options.

³Prolonging treatment to 16-20 wks may be considered in patients with cirrhosis, especially if TE.

⁴This regimen is not recommended for TE patients with cirrhosis.

⁵SOF + RBV for 24 wks may be considered in this situation. As a preferable alternative, SOF + SMV \pm RBV or SOF + DCV \pm RBV may be considered within the framework of early access programs or authorization by Swissmedic as well as reimbursement by health insurances if applicable.

NS3 Q80K testing is available, e.g., at the Laboratory of Virology of the University Hospitals of Geneva (www.hug-ge.ch/sites/interhug/files/structures/gr-demande-analyse/viro-resistance_vhc.pdf) or the Diagnostic Laboratory of the Service of Immunology and Allergy of the CHUV (www.immunologyresearch.ch/ial-bon-50-chuv-lia-immunologie-v12-fr.pdf).

HCV RNA monitoring on treatment

On triple therapy with SOF + PEG-IFN- α + RBV, it is recommended to determine HCV RNA at baseline, week 4 and week 12 (end of treatment), and 12 or 24 weeks after the end of treatment (8).

On IFN-free treatment regimens, it is recommended to determine HCV RNA at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of treatment (8).

Special patient populations

Treatment of patients with chronic hepatitis C awaiting liver transplantation (LT) or with recurrent hepatitis C post-LT, patients with decompensated cirrhosis, patients with end-stage renal failure or on hemodialysis, patients with hemoglobinopathies, and patients with acute hepatitis C should be discussed and pursued with an expert.

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