Hepatitis C Treatment in Patients receiving Opiate Substitution

Recommendations of the Swiss Association for Addiction Medicine (SSAM)

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Summary

Every patient with drug consumption in their medical history should be screened for hepatitis C. The treatment of hepatitis C should be evaluated for individual and epidemiological reasons as well as from a public health perspective in each drug-dependent patient with hepatitis C. Substitution treatment is an ideal basis for hepatitis C treatment in drug addicts. Hepatitis C treatment can easily be performed during opiate substitution and its success is comparable to that in non-drug addicts, regardless of possible parallel use. Important conditions for treatment are a mentally and physically compensated state and the willingness and ability for regular check-ups.

Introduction

These recommendations for hepatitis C treatment are the basis of the shorter version, which is a component of the Clinical Recommendations for Substitution-assisted Treatment (SAT) in Opioid Dependence (www.ssam.ch). It was written by the Swiss Association for Addiction Medicine (SSAM) in consideration of current medical evidence. These guidelines are not legally binding. The recommendations should support the decision process but not replace it and there may certainly be reasons to depart from the recommendations during treatment.

The scientific publications on the SGB were divided into degrees of evidence Ev I to Ev V according to the criteria for Swiss guidelines (Central Board of Directors FMH 1999). In areas where there are only clinical experiences without confirmed scientific examinations, the authors draw on the many years of clinical discussion in Switzerland. The recommendations are divided as follows:

A Recommendation is well-founded empirically: data from several randomized studies or meta-analyses
B Recommendation generally justified; data from randomized or non-randomized studies
C Recommendation proven clinically in individual cases: data from case studies or expert opinions

Recommendations based on studies of Ev I and II were assigned to degree of recommendation [A], those based on studies with Ev III to [B] and those based on studies with Ev IV and V as well as those recommendations rendered as a consensus after the authors' detailed discussion were assigned to degree of recommendation [C].
Background
The number of opiate dependants in Switzerland was estimated between 25,000-35,000 persons in the late 1990s. 16,200 patients were receiving substitution-supported treatment in late 2005. The majority of these patients (88%) received substitution with methadone, 8% with heroin, 3% with Buprenorphine and around 1% with other opiates (morphine, codeine etc.). Intravenous drug users (IVDU) are the largest risk group among patients with chronic hepatitis C [1; 2]. The prevalence among IVDU in Western Europe is between 33 and 98%[3] and among patients in substitution-supported treatment in Switzerland 57%[4]. The peak of hepatitis C (HCV)-induced liver failure will rise by about 2015 despite dropping incidence numbers due to its slow progression over decades[5].

In the future, IVDU will represent the largest group of liver cirrhosis patients and, therefore, of transplantation candidates[6]. This will cause remarkable health care costs. The current national and international guidelines contain controversial recommendations regarding HCV treatment in IVDU[7]. Different studies show comparably good therapeutic results with IVDU during opiate substitution as in patients who were not dependant on drugs[8-11]. However, there is still reluctance regarding hepatitis C treatment in this patient group that is not based on evidence[12]. We counted 77 HCV therapies in 882 patients during opiate substitution in the Swiss hepatitis C cohort study (8.7 %). On the other hand, 485 of a total of 1,092 patients with other routes of infection were also treated (44 %)[13].

The conclusion from the aforementioned circumstances is that hepatitis C therapy in drug patients has to be urgently intensified. The treatment and the associated reduction of the infection sources should also be considered as part of urgent prevention work. These recommendations should help physicians and other persons treating patients with opiate substitution to guarantee adequate diagnostics and care of hepatitis C in this patient group before, during and after treatment.

Transmission path
The hepatitis C viruses are not only transmitted through shared needle use but also through sharing drug preparation utensils (filters, spoons, water etc.) and common inhalation tubes that can cause lesions on the nasal mucous membrane [14; 15] (Ev III).

Screening
The hepatitis C antibodies should be determined annually in each patient with intravenous or pernasal drug use in the medical history (this includes one-time use), independent of high liver parameters, because of the high prevalence [16]. If the antibodies are positive, the viral load must be...
determined (HCV RNA) [16]. If RNA is detectable the genotype must be determined [17] [A].
The indication, treatment and check-ups should be performed by a physician who has experience with hepatitis C [C].

Hepatitis vaccinations
The morbidity and mortality for hepatitis A and B are higher in drug-dependant hepatitis C patients. For this reason the hepatitis A and B titers should be determined in all patients with drug use in their medical history. Hepatitis A and B vaccinations are recommended if the titers are negative [17] [A].

Indications and contraindications

Adherence
The prerequisite for treatment is a stable mental and somatic state that can also be medically adjusted. Furthermore, the patient’s motivation, understanding and the ability to perform regular check-ups and contraception (in men and women) are important [18]. The frequent contacts within the scope of opiate substitution treatment positively influence adherence to appointments and treatment [7]. The adherence of patients receiving opiate substitution is comparable to HCV patients who did not get infected through drug use [19] (Ev II).

Setting
If possible, the dispensing or administration of the medication should be coupled with opiate administration as a result of which possibly monitored taking of medication and frequent patient contacts can be guaranteed [B]. When methadone is dispensed by a pharmacy, close collaboration and consultation with the pharmacy are important in order to guarantee quick dosage adjustments.

Alcohol
High alcohol consumption decreases the efficacy of treatment with pegylated interferon and Ribavirin. This efficacy has a linear correlation with the alcohol amount [20; 21] (Ev I), but it is presumed that the negative influence of alcohol consumption on HCV treatment can be explained by the high termination rate due to non-adherence and not as a direct pharmacological interaction [21] (Ev III). This negative influence can be counteracted to a certain degree by intensive treatment as, for example, opiate substitution.
Alcohol is the most relevant factor on the progression of liver fibrosis and, therefore, the development of liver cirrhosis with all medical and
socioeconomic consequences in untreated hepatitis C patients. Here there is also a linear relationship to the daily alcohol dose [23-25] (Ev 1). A sensible benefit/risk analysis regarding the indication of HCV treatment of alcohol-dependant patients receiving opiate substitution is indicated due to the aforementioned reasons. Alcohol consumption may not be viewed as an absolute contraindication [C].

Intravenous drug use
Intravenous drug use generally does not negatively influence the outcome of a hepatitis C therapy [13; 19; 26; 28] (Ev III). Antiviral therapy should usually not be chosen only in patients with uncontrolled, risky intravenous drug use (Ev IV). However, an individual benefit-risk analysis should be performed as with all other patients [27] [B]. All patients must be informed of the danger of reinfection before the treatment [6]. According to the literature, the reinfection rate after successful treatment is less than half the risk of a new infection [27-30] (Ev II).

Liver biopsy
An ultrasound of the liver and fibrosis staging in which the degree of fibrosis is determined are needed for an indication for hepatitis C therapy. Alternatively to an invasive biopsy, the fibrosis staging can be performed using laboratory parameters (APRI Score, FIB4 score) or a Fibroscan. It is not obligatory to perform a liver biopsy for the indication. The worse the prognosis for successful therapy, the more it is indicated; this is the case for genotype 1 and 4, high viral loads, high parallel alcohol consumption and HCV/HIV coinfections. It is recommended in these cases to perform a liver biopsy to decide what treatment to perform. However, a liver biopsy does not have to be performed with genotype 2 and 3 with high transaminases. In cases of doubt, the indication of a liver biopsy can be discussed with a hepatological center [9] [B]. The non-invasive Fibroscan examination is still being validated and is not yet covered by public health insurance. It measures the stiffness of the liver and allows for a differentiation between different degrees of fibrosis, particularly when advanced, and is also suitable for follow-up examinations [31].

Side effects
Side effects of hepatitis C treatment (type and rate) occur as frequently as in the remaining collective [9] (Ev II).

An examination for symptoms of depression and, at best, starting antidepressant therapy before or during treatment with interferon should be considered due to the frequent mental comorbidities of drug patients. Preventive antidepressant therapy is indicated if a patient has previously had
symptoms of depression or if there is any risk of recurrence of depression based on the medical history [9; 32] [B]. The risk of depression is highest during the first 12 weeks of treatment [33; 34] (Ev I). It is crucial during this time to intervene consistently if there are any signs of depression. Antidepressant therapy should be performed for at least 3 months beyond the antiviral treatment because of mental side effects [35] [B]. The response rates and compliance in patients with previous mental disorders are similar to the comparison groups [36-38] (Ev III).

The dosage of the substitution substance often has to be increased during the initial phase of HCV treatment; the underlying mechanisms of this are unknown [9; 39] [C]. Decreasing the dosage of the substitute (and also of the pegylated interferon and Ribavirin, depending on use of the preparation) can also become necessary if a patient loses weight during treatment. One must be particularly cautious during hepatitis C treatment in the vulnerable phase of the opiate tolerance development with respect to the loss of tolerance at the beginning and end of opiate substitution. If possible, 6 months should elapse before starting hepatitis C therapy after possible opiate withdrawal.

Implementation
The duration of therapy, the dosage and the time between follow-up examinations are the same as in non-drug users (www.sevhep.ch). The prognosis for lasting therapeutic success (no virus detectable 6 months after the end of treatment) is between 40 and 90% depending on the genotype. Intensive, frequent care during treatment, depending on the mental and somatic comorbidity, is sensible for improvement of adherence [C].

Interactions
There are no known interactions between pegylated interferon or Ribavirin and methadone or Buprenorphine [39] (Ev III). Regular determinations of the liver parameters are indicated with simultaneous Buprenorphine substitution [39] [B]. The dosage does not have to be fixed with a stable chronic liver disorder, including liver cirrhosis, despite the hepatic metabolism of methadone (see also Dosing of substitute medication) [C].

Dosing of substitute medication
A patient must be monitored for signs of intoxication in case of acute liver diseases and the dosage must be reduced, if necessary [39] [B]. According to experience, the need for opiates can increase somewhat at the beginning of
HCV treatment, for which reason a temporary increase of the substitute medication dosage is sensible [C].

Specific situations:

HIV/HCV coinfection
85% of all HIV-positive opiate users in Switzerland are coinfected with hepatitis C. The coinfected constitute 8% of the total collective of patients receiving opiate substitution [4].

The mortality due to liver failure has become the second-most frequent cause of death in HIV patients after AIDS. The liver is more frequently becoming the limiting organ during HIV therapy [40; 41] (Ev I). Liver fibrosis rate is significantly higher in the case of coinfection with HIV than with HCV mono-infection. HCV therapy can be performed in the coinfected and should be aimed at [B]. Fibrosis staging should be repeated every 2 years if therapy is not performed [C]. In the case of advanced liver cirrhosis, consistent monitoring regarding liver decompensation has to be performed during treatment [42] [B].

The CD 4 cell status is an important marker when deciding on treatment since the amount of CD 4 cells decreases during HCV therapy. If need be, antiretroviral therapy should be initiated beforehand and HCV treatment delayed until the CD 4 cells have stabilized and the HIV viruses have disappeared [A]. HCV therapy is contraindicated with opportunistic infections [9] [B]. The duration of treatment is 48 weeks and does not depend on the genotype [43-45] [B]. The complex therapy of drug patients coinfected with HIV/HCV should be performed by experienced physicians [C].

Acute Hepatitis C
It is recommended to have patients with acute hepatitis C evaluated at a hepatological center and, if necessary, have them treated there [C]. If possible, these patients should be included in ongoing studies [46-48].

Monotherapy with pegylated interferon for 6 months starting about 3 months after the infection is associated with a high response rate, but studies have shown that the drug users’ adherence to therapy is often limited in these situations [49] [B].

 Decompensated liver cirrhosis
Drug users with liver decompensation due to chronic hepatitis C should also be evaluated regarding the possibility of a liver transplant. The only contraindication for this measure is uncontrolled drug consumption, but not opiate substitution [19; 50; 51] [B].
Literature


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[19] Robaeys G et al. Similar compliance and effect of treatment in chronic hepatitis C resulting from intravenous drug use in comparison with other infection route. Euro J Gastr Hep, 2006; 18: 159-166


