

## **Treatment of Chronic Hepatitis C Virus Infection in Intravenous Drug Addicts: State-of-the-Art**

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### *Summary*

Injection drug users (IDUs) are the largest group of people infected with the hepatitis C virus, and the group among whom most new infections occur. Treating chronic hepatitis C in IDUs is important at an individual level and from a public health perspective. Treatment with a combination of pegylated interferon and ribavirin eradicates the virus in a high percentage of patients depending on the HCV genotype. Unfortunately, HCV-positive IDUs are rarely offered this treatment because of their assumed lower compliance with treatment, psychiatric comorbidities, social discomfort and the risk of reinfection. However, there is increasing evidence that IDUs treated for HCV infection can achieve a sustained virological response comparable to that of non-IDUs. It has also been shown that drug addicts with HCV infection can benefit from anti-HCV treatment if it is given within the framework of a multidisciplinary standardized model of care. In this scenario, prospective clinical trials are warranted to establish new guidelines for the treatment of HCV infection in patients with drug dependence.

Key Words: HCV infection - Treatment - Clinical Issues  
- Drug Dependence

### **Introduction**

Chronic HCV infection is the leading cause of chronic liver diseases, including cirrhosis and cancer; 170 million people worldwide are infected. Injection drug users (IDUs) are the largest group of people infected with hepatitis C virus, and the group among whom most new infections occur. Moreover, IDUs represent a particular challenge in the management of chronic HCV infection because of their assumed lower

degree of adherence to treatment, their psychiatric comorbidities, social discomfort and risk of reinfection. However, treatment of chronic hepatitis C in IDUs is important both at an individual level and from a public health perspective. The National Institutes of Health recognized that drug addiction should not qualify as an *a priori* a criterion for HCV-treatment exclusion, and stressed that management of HCV-infected IDUs is more effective if the patients are enrolled in drug treatment programmes<sup>1</sup>. Given the large body of evidence that IDUs affected by HCV can benefit from treatment<sup>2</sup>, prospective clinical trials are warranted to verify this observation and to establish treatment guidelines for this specific population.

### **Prevalence and Natural History of HCV Infection among IDUs**

The overall prevalence of HCV infection in the general population is estimated to be between 1 and 2.4%, but this rate increases to 40-95% among IDUs in developed countries<sup>3</sup>. The risk of infection is extremely high among IDUs who share needles or other equipment: the percentage of those who become infected is between 50% and 80% after one year of drug use, and nearly all IDUs have become infected after 8 years of drug use<sup>4</sup>.

Active drug users are therefore the primary source of new HCV infections, both within this category of individuals and in the overall population (sexual partners, household contacts, etc.). Moreover, it has been demonstrated that IDUs tend not to change their behaviour after disclosure of HCV infection and continue to be a risk to others<sup>5</sup>. Thus, people with current or past substance abuse should be informed about HCV infection and should be screened for it.

There are very few studies about the natural history of HCV infection in people who pick up the infection from injection drug use, mainly because of methodological concerns. Firstly, IDUs are not usually treated for HCV infection in academic centres, where most natural history studies have been conducted. In addition, IDUs rarely undergo liver biopsy to monitor the stage of liver fibrosis and can be difficult to monitor longitudinally<sup>6</sup>. Rai and colleagues<sup>7</sup> studied the incidence of end-stage liver disease and the clinical expression of cirrhosis in a cohort of 1667 IDUs in Baltimore, and found that severe liver disease is uncommon, especially in young people. Even though HCV infection generally progresses slowly in young IDUs during the first 10 years of infection<sup>7</sup>, its prognosis could be unfavourable because of poor nutritional status, alcohol abuse, multiple infections and superinfection with known or unknown viral agents<sup>8</sup>. Additional research is needed to identify markers of liver fibrosis and to elucidate the mechanism of fibrosis progression in HCV-infected IDUs.

### **Treatment of HCV Infection Among IDUs**

Up to 1998, interferon (IFN)- $\alpha$  was the only effective treatment for HCV infection. In 1998, the combination of IFN- $\alpha$  (administered three times a week subcutaneously)

and ribavirin (in a orally twice a day dose) was found to improve the rate of sustained virological response (defined as negative HCV RNA 6 months after treatment completion)<sup>9,10</sup>. At a later stage, two types of pegylated interferon (INF- $\alpha$ -2a, and INF- $\alpha$ -2b) with a longer half-life became available, and subcutaneous administration was cut down to once a week. Combined therapy with pegylated interferon and ribavirin was reported to be significantly more effective than non-pegylated interferon; it resulted in a sustained virological response in 51-56% of patients with HCV genotypes 1 and 4, and in 76-82% of patients with HCV genotypes 2 and 3<sup>11,12</sup>. Treatment duration differs according to genotype: 48 weeks are required in HCV genotypes 1 and 4, whereas 24 weeks is sufficient in HCV genotypes 2 or 3.

Although the combination of pegylated interferon and ribavirin seems to eradicate the virus in a high percentage of patients, it appears that few HCV-positive IDUs are offered this treatment<sup>13</sup>. Hagan et al.<sup>14</sup> recently concluded that among 404 HCV-positive IDUs aged 18-35, only 4% would be offered treatment if those with problem drinking, moderate-to-severe depression, or recent injection drug use were considered ineligible<sup>14</sup>. It is feared that treatment efficacy among IDUs might be affected by various socio-demographic and behavioural characteristics, namely, a low level of willingness to enter treatment, a poor degree of adherence, adverse events (particularly psychiatric events), psychiatric comorbidities, social discomfort and reinfection<sup>15</sup>. As a result, almost 50% of HCV-infected IDUs do not receive any treatment, despite fulfilling medical criteria for antiviral therapy of chronic hepatitis C<sup>2</sup>. Indeed, in the late 1990s, directives for the management of HCV infection recommended not treating HCV-infected subjects who had a history of active drug addiction<sup>16,17</sup>. It was not until 2002 that the National Institutes of Health declared that drug addiction must not be adopted as an a priori exclusion criterion, and recommended that treatment of drug addicts affected by chronic HCV be associated with detoxification programmes<sup>1</sup>. Two years later, an American Association for the Study of Liver Disease practice guideline recommended that "treatment of HCV infection should not be withheld from persons who currently use illicit drugs or who are on a methadone maintenance program, provided they wish to take HCV treatment and are able and willing to maintain close monitoring and practice contraception"<sup>18</sup>.

These recommendations are based on growing evidence that HCV-infected IDUs can benefit from antiviral treatment. In fact, 36% of abstinent IDUs<sup>(19)</sup> and 54% of patients on maintenance therapy for drug abuse<sup>(20)</sup> achieved a sustained virological response with interferon alone or in combination with ribavirin. This is in line with reviews in which it was concluded that sustained response and acceptance of treatment in patients engaged in detoxification programmes were comparable to those in control groups and to those observed in representative clinically controlled trials<sup>2, 21</sup>. Moreover, in the only prospective study of combined therapy with pegylated-interferon plus ribavirin among patients on methadone maintenance, Mauss and colleagues<sup>22</sup> found no difference in sustained virological response to the treatment combination between patients on methadone maintenance and a control group. However, treatment discontinuation

in the first 8 weeks of therapy was higher in patients on methadone maintenance (22%) than in controls (4%). After the first 8 weeks of therapy, discontinuation rates did not differ between the two groups, and 50% of patients prematurely discontinued treatment in the methadone group.

Although these studies provide evidence for treating HCV-infection in patients with drug dependence, prospective clinical trials are needed to establish anti-HCV treatment guidelines for IDUs that take into account the supposedly lower willingness to undergo treatment, the frequent presence of psychiatric disorders and the risk of reinfection.

### ***Willingness to enter treatment***

As is true of all chronic diseases, the success of chronic HCV infection treatment depends mainly on willingness to accept medication. Among patients with HCV genotype 1, adherence (defined as the use of at least 80% of the prescribed therapy for at least 80% of the expected treatment time) was associated with a greater probability of virological success: 63% of patients who complied with treatment versus 52% who were non-compliant<sup>23</sup>. McHutchison et al.<sup>23</sup> reported a direct relationship between adherence and virological response: adherence levels at least equal to 80% of the prescribed therapy determined an increase in the probability of sustained virological success, namely, from 44% to 52% for therapy with interferon/ribavirin, from 54% to 63% for therapy with pegylated-interferon/ribavirin, and from 61% to 72% for therapy with pegylated-interferon/ribavirin (with dose adjustment according to body weight).

Few studies have investigated the impact of non-adherence to anti-HCV treatment on therapeutic outcomes among IDUs. From the data available on adherence to medication in infectious diseases other than HCV, mainly HIV infection, IDUs were not more likely to refuse treatment than other groups of patients. In a review of predictors and correlates of non-adherence to antiretroviral medication in HIV infection, Ammassari and colleagues<sup>24</sup> reported that a history of intravenous drug use was not consistently associated with non-adherence. This finding was confirmed on the acceptance of anti-HCV therapy. In a prospective study of 50 drug addicts included in maintenance programmes, Backmund et al.<sup>19</sup> reported high percentages of response to therapy and that keeping of at least 2/3 of appointments, which is indicative of a higher degree of adherence, was a predictor of a sustained virological response. Moreover, the report of a good virological response in subjects with drug dependence<sup>25</sup> suggests that good levels of adherence can be achieved in this subset of patients, particularly when medical care is well integrated with treatment for substance abuse.

Important issues include the correlates and predictors of non-adherence to anti-HCV treatment among IDUs. Non-adherence to treatment is now recognized to be an extremely complex phenomenon involving factors related to the patient, the disease, its therapy and the physician-patient relationship<sup>24</sup>. Psychiatric comorbidities and depression disorders play a particularly important role in adherence to treatment among HCV-infected IDUs, because of their high prevalence in this setting and the implications at a behavioural level.

For chronic diseases other than HCV infection, it is well documented that depres-

sion is an important risk factor for non-adherence to treatment: in a meta-analysis that examined the impact of depression on attitude and adherence to treatment, depressed patients had a risk of non-adherence that was three times higher than that of patients without depression<sup>26</sup>. Various studies, including a cohort study of Italian patients<sup>27,28</sup>, have demonstrated a correlation between depression and non-adherence to antiretroviral drugs<sup>29-32</sup>. In addition, more severe depressive symptoms were associated with an increased risk of disease progression and death, independently of socio-demographic characteristics, drug abuse and other clinical variables<sup>33</sup>. Nevertheless, because most of these studies were cross-sectional, we cannot draw causal inferences about the association between depression and non-adherence to treatment.

The relationship between depressive disorders and adherence to therapy has not been widely studied in the context of anti-HCV therapy. In a prospective study of therapeutic efficacy, adherence to treatment and neuropsychiatric side-effects, Schaefer et al.<sup>34</sup> did not find any significant difference in the endpoints between a group of patients with previous psychiatric disease and control groups. Interestingly, the incidence of drop-outs and therapy discontinuation was lowest in patients with a psychiatric history; indeed, none had to discontinue treatment because of neuropsychiatric side-effects. We recently investigated the impact of depression disorders and self-reported adherence to treatment on the effectiveness of anti-HCV antiviral therapy. The investigation was conducted within the framework of the Nocchiero study, which is an Italian multicentre prospective cohort study on the efficacy and tolerability of the treatment of HCV-infection with pegylated-interferon alpha-2b and ribavirin in interferon-naïve drug addicts receiving opioid maintenance therapy<sup>35</sup>. It was conducted in collaboration between 11 detoxification units (National Health Service Managed Drug Treatment Services; SerT), and 6 clinical centres for the management and care of infectious diseases and HCV. Out of 53 patients enrolled in the study, 43 patients completed a self-report questionnaire about depression symptoms (Centre for Epidemiological Studies–Depression Scale; CES-D). In this subgroup, 28.1% of patients reported attitudes of non-adherence; in 12.5% of these cases, non-adherence was directed to pegylated-interferon, in 21.9% to ribavirin, and in 6.3% to both drugs. The higher rates of non-adherence to ribavirin versus interferon may be because interferon was given weekly at the SerT, whereas ribavirin was taken by the patients themselves. We did not find that depression symptoms evaluated at the beginning of treatment significantly affected adherence, at least as far as the first quarter of therapy was concerned. This result is important, because good adherence in the first three months of therapy results in an early virological response, which, in its turn, is associated with a sustained response<sup>36,37</sup>.

Taken together, these findings suggest that individualized programmes designed to address the particular needs of IDUs, and integrate medical care with treatment for substance abuse can achieve high rates of adherence.

#### ***Tolerability and side-effects***

Combined interferon and ribavirin treatment for HCV infection is complex and is associated with adverse reactions. In the registration trial of pegylated interferon and

ribavirin, side-effects caused treatment discontinuation in 10-14% of patients<sup>11,12</sup>. The major side effects of the combination therapy are flu-like symptoms, haematological abnormalities, and neuropsychiatric symptoms. Up to 50% of patients receiving treatment with interferon may experience adverse neuropsychiatric effects, especially depression<sup>38,39</sup>. Other adverse neuropsychiatric effects are anxiety, cognitive slowing, impaired concentration and insomnia, all of which are also symptoms of a major depressive disorder.

Neuropsychiatric disorders, especially depression, are the most challenging side-effects when treating IDUs because of the high prevalence of pre-existing or concomitant psychiatric problems in these patients and the potential for a detrimental effect on adherence to treatment.

Comorbid psychiatric symptoms and drug abuse are the most frequent reasons not to treat IDUs for HCV infection<sup>40,41</sup>. These exclusion criteria were adopted because of concerns that interferon may worsen underlying psychiatric illness, which could result in premature discontinuation of antiviral treatment, non-adherence to treatment, suicide, and violence toward others. However, it is now recognized that patients with stable psychiatric illness who are engaged in mental health treatment can successfully complete treatment with interferon for HCV infection<sup>1</sup>. In a prospective study of therapeutic efficacy, adherence to treatment and neuropsychiatric side-effects after HCV treatment in former drug addicts, methadone-replacement subjects, and patients with severe chronic psychiatric disorders versus an HCV-infected control group, there were no differences in the study endpoints between patients with previous psychiatric disease and the control group<sup>34</sup>. Moreover, antidepressant treatment seems to be effective in preventing major interferon-associated depression in HCV-infected patients<sup>42</sup>. However, larger, controlled randomized trials are required to verify if this strategy results in a better response to antiviral therapy.

In the Nocchiero Study, when we investigated the impact of self-reported depression disorders (through the CES-D scale) on the effectiveness of anti-HCV antiviral therapy<sup>35</sup>, we found that the mean CES-D score at enrolment (17.3 SD  $\pm$  11.06) did not change substantially after 4 (mean: 19.1; SD+10.9) or after 12 (mean: 17.8; SD+10.4) weeks of HCV therapy, and did not impair the virological response to therapy during the first 3 weeks of treatment. Patients who clearly showed a depressive attitude had a significantly higher grading of symptoms and/or side-effects (mean: 14.2  $\pm$  4.46 SD) than patients with a CES-D score below 16 (mean: 7.42  $\pm$  3.82 SD; t-test  $P < 0.0001$ ). Moreover, self-reported side-effects were associated with early discontinuation of anti-HCV treatment. Indeed, subjects reporting a higher symptoms/side-effects score had a greater probability of early treatment discontinuation (OR 1.33; 95% CI 1.02–1.71;  $P=0.03$ ) than did subjects reporting a lower score. A previous study of IDUs affected by acute hepatitis C showed that patients experiencing or fearing side-effects were at a greater risk of treatment refusal and/or premature withdrawal<sup>43</sup>.

These findings highlight the relevance of subjectively identified symptoms, regardless of their clinical importance, and suggest that the management of side-effects is

critical to treatment efficacy during the first weeks of therapy. A symptom checklist drawn up by patients would help to identify the onset of side-effects and be helpful to physicians in guiding their dialogue with patients regarding these symptoms, their causes, and possible treatment. This approach may be particularly useful for difficult-to-treat patients such as drug abusers.

### **Risk of Reinfection**

A major concern about treating HCV infection among IDUs is that patients in whom the virus has been eradicated may become re-infected. HCV infection does not confer protective immunity, and cases of reinfection have been reported<sup>44,45</sup>. Therefore, patients who continue to be exposed to the virus risk reinfection, and this risk is estimated to be the same as that for drug users who have never been infected<sup>46</sup>. In a study of the frequency of superinfection among highly exposed IDUs, Herring and colleagues<sup>47</sup> reported that HCV superinfection in IDUs, both intra- and inter-genotype, is a frequent event (20% in the cohort), with an incidence rate similar to that of first-time infections. This finding suggests that no cross-protecting immunity develops during the first year of chronic infection with HCV<sup>47</sup>. Although the real prevalence<sup>48</sup> and clinical consequences of HCV superinfection remain unknown, it should be stressed that infected persons and those whose viremia has been eradicated by antiviral therapy should protect themselves against subsequent HCV exposure.

### **A Model Integrating Drug Abuse Detoxification and HCV-Treatment**

Previous studies<sup>49,50</sup> and our own experience indicate that an effective strategy in the treatment of HCV infection in IDUs is to start treatment during detoxification or methadone maintenance, under the supervision of physicians specialized in hepatology and addiction medicine.

In this context, we devised and applied a strategic standardized model that integrates drug abuse detoxification and HCV treatment. We first identified multidisciplinary teams made up of specialists in infectious diseases from 6 reference clinical centres, specialists in the treatment of drug addiction (working in detoxification services: SerTs), a consultant psychologist or psychiatrist and at least one nurse from each reference site and from each SerT. Six teams were identified. Representatives of the clinical centres and SerTs drew up a standardized protocol for the management of antiviral treatment. After a preliminary phase in which the methodology was shared and regular meetings were scheduled to monitor teamwork, each SerT identified subjects engaged in addiction therapy programmes who had known for at least six months that they were anti-HCV-positive. These subjects were offered screening to confirm viral infection and to assess the severity of chronic HCV hepatic disease. Subjects identified in the preliminary screening received counselling about their health status, the characteristics and risks of the natural history of chronic C hepatitis, and the benefits and potential side-effects of antiviral treatment. They were then referred to the reference clinical centre for more detailed screening (HCV RNA definition, genotype analysis and assessment of bio-hu-

moral and immunological parameters to verify treatment eligibility), for clinical evaluation and liver biopsy. When chronic hepatitis was diagnosed and counter-indications to treatment were excluded, the reference clinical centre prescribed anti-HCV treatment and the patient underwent pre-treatment screening for depression with the CES-D. The IDU was then referred back to the SerT and started treatment with pegylated-interferon, administered subcutaneously once a week at the SerT, and ribavirin treatment, which was taken daily at home. The SerT also monitored laboratory parameters, side-effects, treatment adherence and depression symptoms. The SerT referred subjects to the clinical reference site for clinical controls during treatment and follow-up.

In this multidisciplinary team setting, specialists with different types of competence promote good relations with the health care structure by helping drug addicts with their problems. The collaboration between specialists in infectious diseases and in addiction medicine, as well as psychologists, allows us to assess a patient's "readiness" to start treatment and to ensure support for the patient throughout the treatment programme. Patients were informed about the rationale and terms of therapy, and about the potential for the onset of adverse effects. Moreover, the weekly consultation at the SerT provided an opportunity to monitor and reinforce motivation, and adherence to treatment.

Through this multidisciplinary approach, we treated 53 IDUs engaged in detoxification programmes. The results were very satisfactory, namely, 58.5% of patients had an end-of-treatment virological response, and 54.7% a sustained virological response.

In conclusion, based on previous studies and our own experience, it should be stressed that drug addicts with HCV infection may benefit from anti-HCV treatment if this is given within the framework of a multidisciplinary standardized model of care. Moreover, our results support the feasibility and efficacy of a multidisciplinary standardized model of care in treating chronic hepatitis C among drug addicts.

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### **Appendix**

The participants in the "Nocchiero" study groups are listed below:

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