

## Liver Disease In MMT: Treatment & Transplant, from Addiction Forum On-line Newsletter



### Hepatitis C - A "Giant Silent Killer"

In merely a decade, researchers have gone from characterizing hepatitis C (HCV) as a "sleeping giant"[1] to an "awakening giant." [2] Meanwhile, many others have called it a "silent killer."

The first article of this series[3] noted that about 9 out of 10 of persons entering methadone maintenance treatment (MMT) programs are likely to be infected with HCV. Of those, roughly three-quarters will develop chronic liver disease.

Although there appear to be many barriers to HCV treatment for MMT patients, there also is cause for hopeful optimism.

### Treatments Improving

HCV treatments continue to evolve and improve, and treatment outcomes are determined by measuring virus particles in the blood. The absence of virus at the end of HCV therapy, called an end-of-treatment response (ETR), is a preliminary sign of treatment effectiveness.

However, a more accurate indicator is the sustained virologic response (SVR). This is defined as the absence of virus 6 months after the completion of treatment, which some describe as a cure.[4]

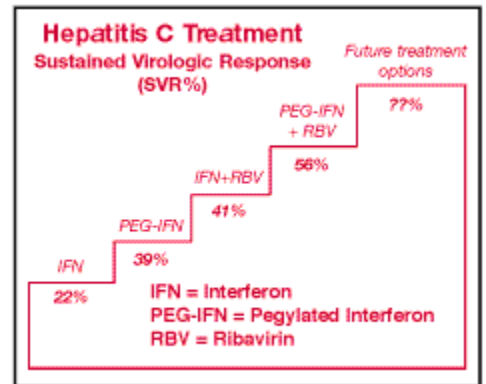
The first treatment for HCV was interferon. Injected under the skin 3 times a week for 24 to 48 weeks, it produced an SVR of up to 22% (**see graph**). The addition of another medication called ribavirin, which is taken by mouth twice daily, led to a near doubling of response rates to 41%.[6,7]

More recently, a longer-acting interferon, called pegylated interferon, has been developed that only requires weekly injection. It is a more effective medication than standard interferon, leading to SVRs of 39% by itself and up to 56% when combined with ribavirin.[8-10]

### Success Factors

The most important predictor of treatment response is a viral characteristic called genotype, a genetic variation that has been likened to a viral "strain." There are 6 major genotypes; in the U.S. genotypes 1, 2, and 3 are the most common, with most patients having type 1.[6]

Genotype does not affect the progression of liver disease, but it has a major impact on treatment outcome. Patients with genotypes 2 and 3 may show SVRs greater than 80% with pegylated



interferon plus ribavirin, but response in those with genotype 1 is only about half that.[11,12]

Additionally, patients staying on therapy and taking nearly all of their medication have better treatment outcomes. [9,10,13] Other factors – such as age, sex, and extent of liver damage – also play a role.[14]

Although eliminating the virus is the main objective of HCV therapy, interferon may benefit the liver even in the absence of viral remission. Some studies have shown that it can slow progression of liver scarring and that it may reduce the risk of developing liver cancer.[15]

#### Unfounded Treatment Barriers

Even though injection drug use (IDU) accounts for the majority of HCV cases, recovering IDUs on methadone maintenance are sometimes denied treatment for HCV and have been excluded from the majority of clinical studies of HCV treatments.[16] Although there is no relevant data, questions are often raised about their ability to tolerate treatment, potential relapse to drug abuse, comorbid psychiatric conditions, and possibility of reinfection.

In the general population, more than 20% of patients may discontinue HCV treatment due to intolerable side effects, including flu-like symptoms, fatigue, and anemia. Interferon can lead to severe depression, and uncontrolled depression or other psychiatric conditions usually exclude patients from starting interferon-based therapy.

An ongoing question is whether MMT patients should be withdrawn from methadone prior to HCV treatment. However, a review by Mattick and Hall [18] concluded that methadone provides stability in patients' lives, making them more receptive to adjunctive therapies. *They specifically recommended that patients need not be taken off methadone before undergoing other therapies.*

A small, prospective study in Europe by Schaefer [19] examined psychiatric complications during combination interferon/ribavirin therapy for HCV in MMT patients compared with control patients who were not former drug addicts. Depression increased equally in both groups of patients; however, the depression was mild to moderate in the methadone patients, whereas severe depression was experienced by a third of the controls. Withdrawals from treatment were equivalent in both groups; none due to depression.

Furthermore, methadone maintenance may slow the progression of HCV infection. An investigation of 285 HCV-positive IDUs [20] found that those in MMT programs were significantly less likely to develop chronic HCV infection than still-active injection-drug abusers. Furthermore, in those already chronically infected, methadone therapy was associated with more normal liver function, and methadone may allow the reversal of heroin-related immunologic impairment. Additional research is needed to better understand the natural history of HCV in MMT patients and the role of methadone in HCV treatment outcomes.

#### Research Supports MMT

In Schaefer's report, mentioned above, the response to interferon/ribavirin therapy after 24 weeks was 50% in MMT patients and 39% in controls. Importantly, during anti-HCV treatment, MMT patients benefited from increased methadone doses.[19]

Blechman and colleagues [17] compared interferon therapy in MMT patients and in a control group of patients not on methadone. Disease severity, response to interferon, side effects, and treatment compliance were similar in both groups. The authors concluded that *MMT patients should not be automatically excluded from HCV-treatment trials and should be offered HCV therapy like anybody else.*

An ongoing series of clinical trials focusing on HCV therapies in MMT patients is being conducted at the Organization to Achieve Solutions in Substance Abuse (O.A.S.I.S.) in Oakland, CA, under

the direction of Diana Sylvestre.[5,21,22] In a preliminary analysis of 57 MMT patients who had completed interferon/ribavirin treatment,[5] the overall ETR rate was 56%; which was comparable to results in non-opioid-dependent populations. Sustained response rates in Sylvestre's study are not yet available.

Occasional drug or alcohol use during this study produced only minor decreases in treatment outcome that were not statistically significant. However, patients using illicit drugs daily showed no virologic response at all to HCV therapy.

Interestingly, the response rate in MMT patients was unaffected by prior psychiatric diagnoses. However, by the end of treatment, 88% of subjects had received some form of psychiatric medication, primarily SSRIs, for depression. Forty-two percent increased their daily methadone dose by an average of 10 mg.

Only 22% of MMT patients discontinued from Sylvestre's study, compared with up to 21% in other studies. However, discontinuations were lower in MMT patients due solely to side effects.

Sylvestre concluded that tolerability, safety, compliance, and response rates in MMT patients were similar to those of historical controls (non-opioid-dependent patients) receiving identical therapy. This was evident despite substantial preexisting psychiatric comorbidity in the MMT patients, and the fact that they were older, and had longer histories of HCV infection along with more liver fibrosis than subjects in other studies. Clearly, the stabilizing effect of MMT in these studies contradicts the need for pretreatment methadone withdrawal.

#### Brighter Prospects

Prospects for MMT patients with HCV are looking brighter and an HCV "giant slayer" may be on the horizon. Sylvestre and her team at O.A.S.I.S. are continuing their research in MMT patients, using the newer pegylated interferon. Clinical trials at the San Francisco VA Medical Center also are enrolling methadone-maintained patients.

Future treatments may include anti-HCV agents that are especially useful in difficult cases. Pegylated interferon has demonstrated improved effectiveness, and a novel, bioengineered "consensus interferon" has shown promise in treating nonresponders. "Triple therapies" including an interferon in various combinations with ribavirin, mycophenolate mofetil, or amantadine have been explored.[11] Unfortunately, non-interferon-based regimens are not expected in the near future, so further study is needed to improve outcomes in difficult patient populations.

Use of complementary and alternative medicines by a third of patients with chronic liver disease has been reported. Silymarin (milk thistle) compounds are frequently mentioned, as are St. John's wort, ginkgo biloba, ginseng, garlic extract, and echinacea.[23]

Most of these agents are used in hopes of minimizing liver damage caused by HCV and to manage treatment side effects. However, the National Center for Complementary and Alternative Medicine is careful to note that "no complementary medicine or alternative medicine therapies have been scientifically proven to cure or even ease symptoms of hepatitis C." [24]

There is still the question of how MMT programs can participate in helping their HCV-positive patients get proper treatment. This will be addressed in the next article of this series.

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