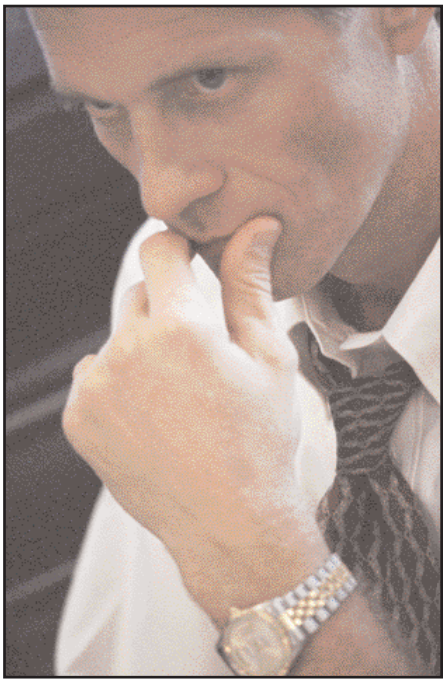
Hepatitis C: What's New?



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In this article:

Mr. Law's hepatitis

Mr. Law, 43, presents for a routine annual checkup. He is asymptomatic, and his physical examination is normal. Serum chemistries reveal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values that are two to three times the upper limit of normal.

He is a social drinker, and agrees to refrain from drinking for three months, but his transaminases remain elevated. He denies any risk factors for viral hepatitis, but serology for hepatitis C is reported to be positive. After further questioning, he remembers using injection drugs once at a party when he was 19. He is aware that some of his old friends have hepatitis C. One of those friends died of cirrhosis.

Now he is very concerned and wants to know if he's going to die, and if he can get rid of his hepatitis C.

Hepatitis C virus (HCV) is a common chronic viral infection, and is one of the most important causes of liver disease in Canada and worldwide. Updated National Institutes of Health guidelines for management of HCV were published recently, and Canadian guidelines will be updated in the fall of 2003.[1,2]

How common is HCV?

HCV was identified in 1989 and a diagnostic test followed soon thereafter.[3] Six major genotypes of this ribonucleic acid (RNA) virus have been identified. In Canada, genotype 1 is responsible for up to 75%, and genotypes 2 and 3 for up to 25% of all infections. Genotypes 4 to 6 are rare in Canada. While genotype does not appear to influence the natural history of hepatitis C, it is the most important determinant of response to treatment.

In Canada, it is estimated that 0.8% of the population, or 240,000 individuals, are infected with HCV. Transmission occurs through parenteral, sexual or perinatal exposure to infected blood. Injection drug use, and receipt of blood products prior to 1992 are the major risk factors for HCV in Canada. Sexual and perinatal transmissions occur, but they are uncommon.

Hepatitis C

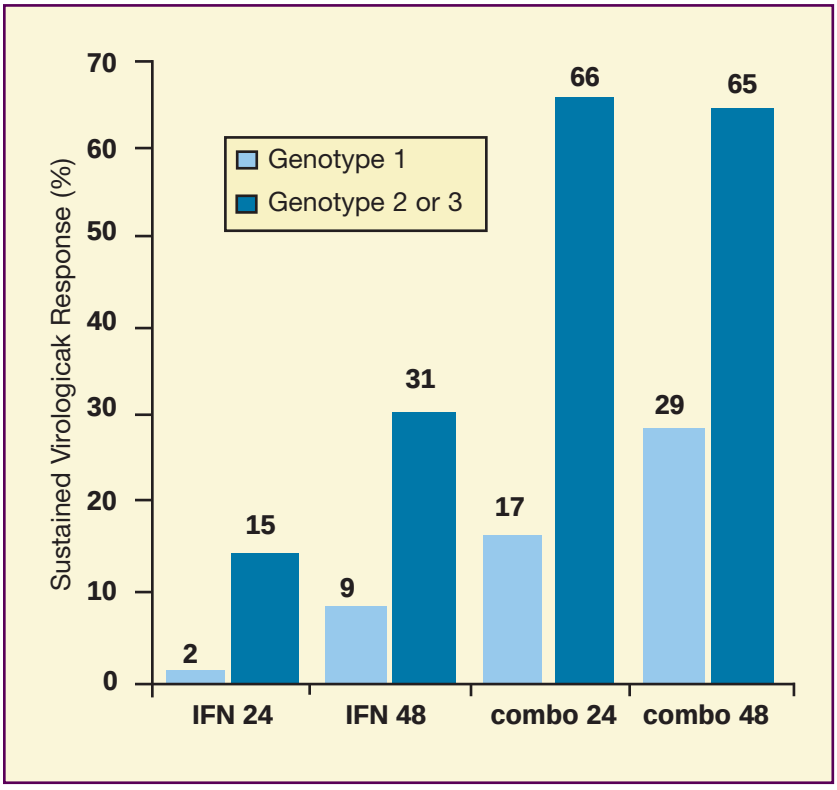

Figure 1. Sustained response to conventional interferon (IFN) therapy alone or with ribavirin (combo) for 24 weeks or 48 weeks, by genotype.

What happens following HCV infection?

Approximately seven weeks (range three to 20 weeks) following HCV infection, 10% to 20% of individuals develop symptoms indistinguishable from other causes of acute hepatitis. Thus, most individuals remain asymptomatic and unaware of their infection. HCV RNA can be detected in serum one to two weeks following infection, while abnormal transaminases appear at about four weeks, and anti-HCV antibody between eight and 12 weeks. In those with chronic hepatitis, HCV RNA remains detectable in serum as a marker of ongoing viral replication. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are elevated in most patients with chronic HCV, but levels correlate poorly with the extent of underlying liver disease.

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What is the risk of end-stage liver disease?

The natural history of hepatitis C remains incompletely defined.[4] Many acute infections resolve spontaneously, particularly in young women.[5] Most patients (60% to 85%) with HCV, develop chronic hepatitis, as evidenced by detection of HCV RNA in serum at least six months following acute infection. Up to 30% of individuals with chronic HCV have persistently normal transaminases and, in general, this group of patients has mild liver disease. The remaining patients have moderate to severe chronic hepatitis characterized by fluctuating liver enzymes (usually in the 1.5 to five times normal range), and may progress to end-stage liver disease and hepatocellular carcinoma. While the risk of progression appears to vary in different patient populations, and limited data are available beyond 20 years of infection, it appears that approximately 10% to 20% of patients ultimately develop cirrhosis. While the risk of end-stage liver disease is low for most patients infected with HCV, the prevalence of this infection makes it a common cause of cirrhosis, and the most common indication for liver transplantation in most centres (Table 2).

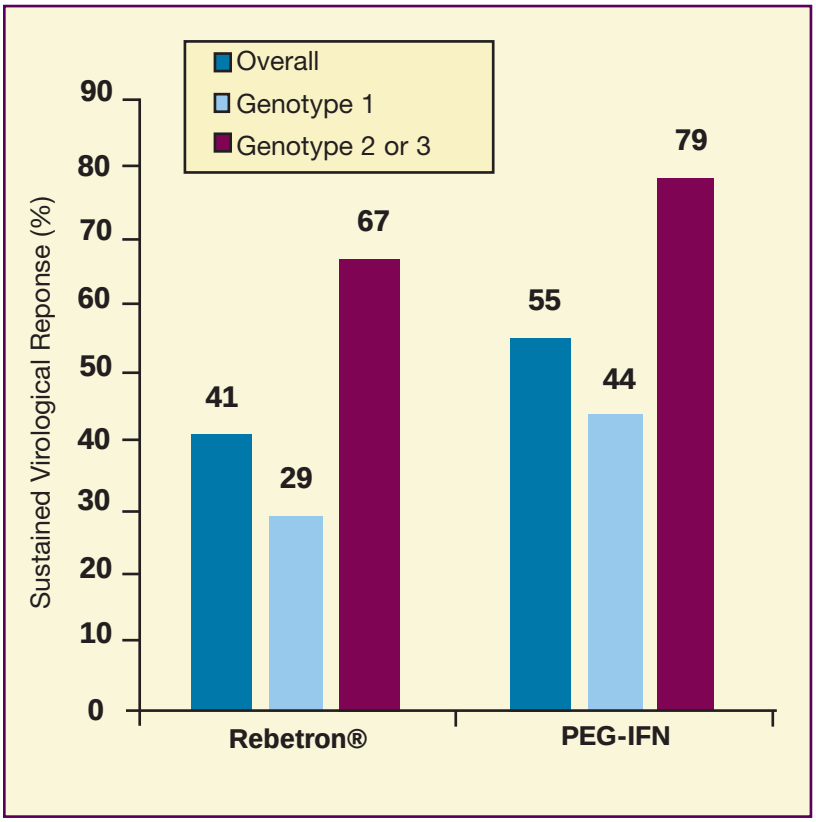

Figure 2. Comparison of pegylated interferons with conventional interferon in combination treatment of hepatitis C for 48 weeks.

How do I manage patients with HCV?

The primary goal of therapy for HCV is eradication of the chronic viral infection. A sustained virological response (SVR) is achieved when HCV RNA is undetectable in serum 24 weeks following completion of therapy, and appears to be durable as only 1% to 2% relapse over several years. In addition, accumulating evidence suggests that therapy may delay or prevent disease progression, improve liver histology, reduce the risk of hepatocellular carcinoma and improve health-related quality of life (particularly if SVR is achieved).[6]

While acute HCV is recognized infrequently, it is of particular concern to health-care workers exposed to blood from patients with chronic HCV. Jaeckel et al. demonstrated that 42 of 43 (98%) of patients treated for acute HCV with interferon (IFN) monotherapy eradicated their infection.[7] Thus, therapy for acute HCV can be very effective. However, the optimal time to start therapy and the choice of therapy remain to be defined.

IFN therapy was investigated for the treatment of non-A, non-B hepatitis prior to identification of HCV. A major advance in the treatment of HCV occurred when two large trials demonstrated improved efficacy of subcutaneous IFN when given in combination with oral ribavirin.[8,9] Combination therapy with IFN alpha-2b 3 MU sc tiw together with oral ribavirin 1000 mg daily

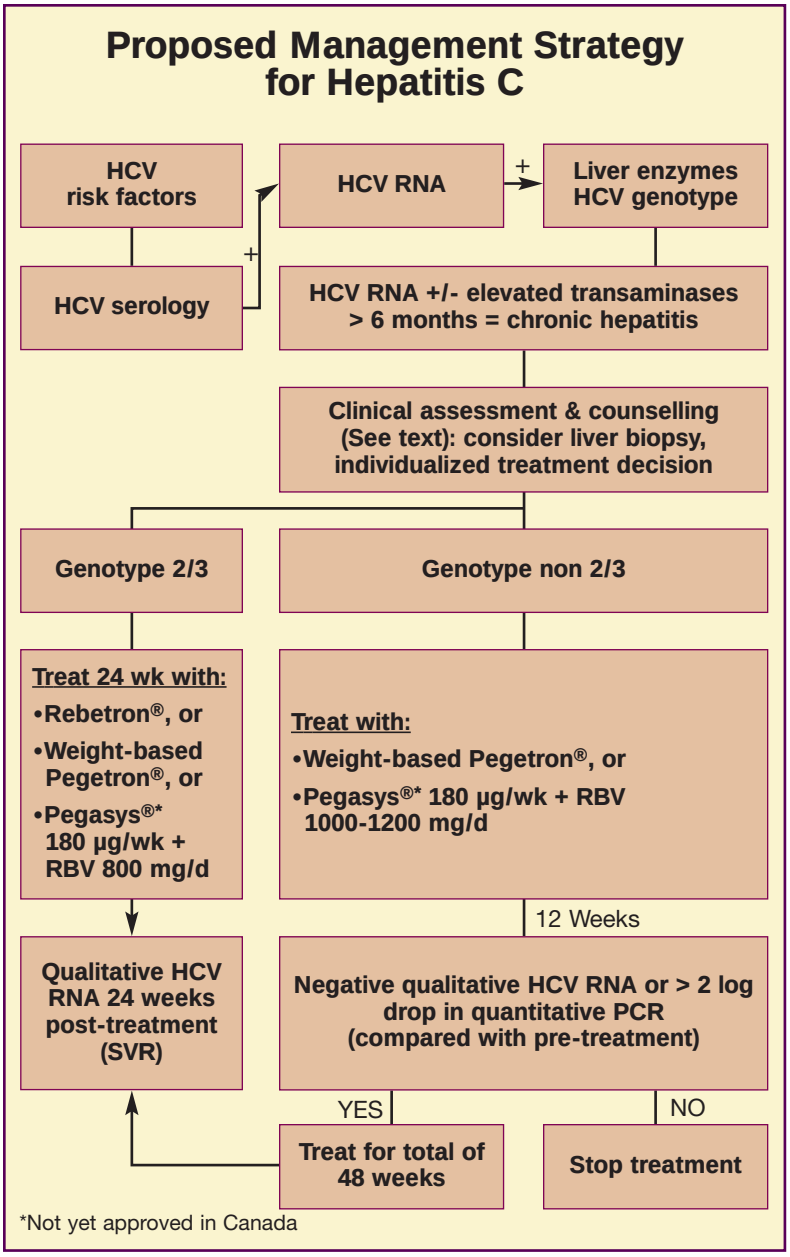

Figure 3. Proposed management strategy for hepatitis C.

(< 75 kg) or 1200 mg daily (> 75 kg), became the standard of therapy in 1998.[2] Overall, 41% of patients achieved a SVR, and HCV genotype was the major predictor of response to therapy. SVR was attained in 66% of patients with genotypes 2 or 3 treated with 24 weeks of combination therapy while 29% of those with genotype 1, the most common strain in Canada, had a SVR with 48 weeks of therapy (Figure 1).

Recently, therapy for HCV has taken another quantum leap with the introduction of pegylated IFN (Peg-IFN). Pegylation links recombinant IFN to ethylene glycol to prolong the half-life of IFN, sustain therapeutic levels, and allow for once-weekly dosing. Two formulations of Peg-IFN have been developed. A smaller 12 kDa IFN alpha-2b molecule is dosed in a weight-based fashion, 1.5 µg/kg per week, and is licensed in Canada in combination with ribavirin. A larger 40 kDa Peg-IFN alpha-2a is dosed at 180 µg/week (Pegasys®). This product is awaiting approval in Canada.

Initial studies showed that Peg-IFN dosed weekly was approximately twice as effective as conventional IFN dosed three times weekly.[10] Two large studies examining the efficacy of Peg-IFN plus ribavirin in treatment-naive patients have now been published.[11,12] Overall results of these two studies are similar and have been combined in Figure 2. SVR rates of 42% to 46% with 48 weeks of treatment for genotype 1 represent a significant advance over conventional IFN therapy. It is not yet clear if SVR rates of 76% to 82% for genotypes 2 and 3 are a significant improvement, though once-weekly dosing may enhance adherence and be preferred by many patients. A post-hoc analysis of the 12 kDa Peg-IFN trial revealed overall SVR rates of up to 61% (48% for genotype 1 and 88% for genotype 2 and 3) if patients received a ribavirin dose of at least 10.6 mg/kg/day.[11] A third large study of the 40 kDa Peg-IFN has shown that 24 weeks of therapy with a reduced ribavirin dosage of 800 mg a day was effective for patients with genotypes 2 and 3.[13]

Adverse effects of Peg-IFN-based therapy are very similar to those of conventional IFN. Flu-like

Getting back to Mr. Law

Mr. Law was likely infected through injection drug use at age 19 though other risk factors should be sought. (Hepatitis C is highly infectious and is acquired early after initiation of injection drug use.) Thus, he has been infected for approximately 24 years. His elevated transaminases suggest that he has chronic hepatitis C. This should be confirmed by detection of HCV RNA in serum. Other virologic, metabolic and immunologic causes of chronic hepatitis also need to be considered in patients with persistent transaminase elevation.

He can be reassured that most patients with HCV pursue a benign course with 10-20% progressing to cirrhosis. Unfortunately, it is not yet possible to predict the rate of hepatic fibrosis and the precise natural history for any individual patient. Older age at infection, male sex, moderate-heavy alcohol consumption, and co-infection with HIV are the risk factors most commonly associated with accelerated progression.

HCV genotype is the most important predictor of response to treatment, and the majority of patients can expect to achieve a sustained virologic response with currently available therapy. Mr. Law should be counseled as outlined in Table 1, and evaluated as detailed in Figure 3.

reactions (including fever, rigors, headache, arthralgias, myalgias, and anorexia) are common and tend to diminish with continued treatment. Cytopenias involving all three lineages are common, and need to be monitored carefully. Neutropenia appears to be more common with Peg-IFN than standard IFN, and is a frequent reason for dose modification. Support with hematopoietic growth factors may prove beneficial. Neuropsychiatric side-effects, including depression, are also relatively common and can be insidious and should be monitored carefully. Judicious use of antidepressant therapy can assist patients to complete their course of therapy. Injection site reactions, including erythema and tenderness, are more common with Peg-IFN than standard IFN but do not generally interfere with a course of treatment. While adverse effects are common, most patients (approximately 85%) will complete the course of therapy.

Given the uncertain natural history of HCV, the expense and relative toxicity of therapy, management strategies must be individualized and continue to evolve. Every patient with chronic HCV should be counselled and vaccinated (Table 1). Patients with detectable HCV RNA in serum and evidence of active liver disease (elevation in transaminases, and/or a liver biopsy) are potential candidates for antiviral therapy. Therapy should be offered if it is likely patients will develop advanced liver disease within their anticipated life expectancy. Patients most likely to develop cirrhosis are those with moderate to severe inflammatory, or fibrotic changes on liver biopsy. A biopsy is useful in grading inflammatory changes and

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Table 1
What to tell your patients with HCV

- HCV is a chronic infection of the liver. Most individuals with HCV will not develop serious liver disease.
- Do not donate blood, organs, tissues, or semen if you have HCV.
- Be careful when handling items that may be contaminated with blood (*e.g.,* razors, toothbrushes and nail clippers).
- The risk of sexual transmission of HCV is low, but not zero. In monogamous relationships, condoms are not felt to be necessary, as the rate of sexual transmission of HCV is very low. For non-monogamous relationships, condoms should always be used to prevent sexually transmitted diseases, including HIV.
- Alcohol and HCV are a dangerous combination. Safe lower limits of alcohol have not been defined.
- Those at risk of HCV should be tested for HIV.
- Everyone with HCV should be vaccinated for HAV. Those at risk for HBV (through non-monagamous sex or use of injection drugs) should be vaccinated against HBV. Testing first can determine whether individuals are already immune to HAV and/or HBV.

HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
HAV: Hepatitis A virus
HBV: Hepatitis B virus

Table 2
Risk factors for progressive liver disease

- Male gender
- Older age at infection
- Consumption of more than two standard alcoholic drinks per day
- Immune suppression, particularly human immunodeficiency virus co-infection.

Seeff LB: Natural history of chronic hepatitis C. Hepatol 2002; 36(5 Suppl):S35-46.

staging fibrosis, while excluding other causes of liver disease. While liver biopsy has been advocated prior to initiating therapy, its role diminishes as therapy improves.[2] Biopsy may not be needed for most patients with genotypes 2 and 3, as approximately 80% of such patients can be successfully treated with currently available therapy. Liver biopsy may help to guide treatment choices in patients with genotype 1. Patients with minimal to mild histologic changes may choose to defer treatment, anticipating more efficacious and less toxic future therapy. Patients most likely to respond to IFN-based regimens are those with genotype 2 or 3, low viral loads, limited fibrosis on liver biopsy, and lower body weight.[6] Absolute contraindications to currently available therapy include:

- decompensated liver disease,
- active alcohol abuse,
- pregnancy or lack of appropriate contraception,
- renal failure, and
- expected non-compliance.

Relative contraindications include:

- ischemic vascular disease,
- untreated depression or psychotic illness,
- uncontrolled seizure disorder, and
- active autoimmune diseases.[2]

Take-home message

Quick facts about hepatitis C virus:

- In Canada, it is estimated that 0.8 % of the population (240,000 individuals) are infected with HCV.
- Transmission occurs through parenteral, sexual, or perinatal exposure to infected blood.
- Injection drug use, and receipt of blood products prior to 1992 are the major risk factors for HCV in Canada.
- Sexual and perinatal transmissions occur, but are uncommon.

What does the future hold?

While many advances have been made in the management of HCV, and the majority of patients can now be successfully treated, numerous questions remain. More information is required regarding optimal dosing and monitoring of Peg-IFN and ribavirin, particularly in patient subgroups, such as those with low or high viral loads, normal ALTs, and cirrhosis.

Future research will hopefully lead to new generations of specific antiviral treatment for HCV with improved efficacy and adverse effect profile and to a vaccine for prevention of the virus. CME

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Net Readings

1. Ready to Learn All About Hepatitis C: www.all-about-hepatitisc.com
2. Centers for Disease Control and Prevention: www.cdc.gov/ncidod/diseases/hepatitis/c/
3. Hepatitis C: An Epidemic For Anyone: www.epidemic.org/index2.html

www.stacommunications.com

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See page 23 for Frequently Asked Questions on hepatitis C virus.