Treatment Options in Patients with Chronic Hepatitis C

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Hepatitis C is a major health care problem plagued by the lack of a truly effective therapy. To date, the combination of interferon and ribavirin has provided the best chance of viral eradication. However, this therapy is expensive, has multiple side effects and works in less than half of patients. New strategies need to be developed to deal with the increasing burden of hepatitis C-related disease, and we anxiously await the arrival of new drugs such as helicase and protease inhibitors.

Hepatitis C (HCV) is a leading cause of chronic liver disease and a major public health problem. An estimated 170 million people are infected worldwide,[1] approximately 270,000 in Canada. The societal and health care burden of this epidemic looms large. Hepatitis C will lead to cirrhosis in up to 20% of people after 20 years of infection.[1] It is a major cause of hepatocellular carcinoma and HCV has surpassed alcoholic liver disease as the leading cause for liver transplantation in North America. In the United States, as many as 10,000-12,000 deaths occur annually as a direct result of HCV. As the cohort of persons infected with HCV by intravenous drug use in the 1960s and 70s ages, this number will certainly increase and some estimate it may triple over the next 10 to 20 years. As we have no effective vaccination strategy against the HCV epidemic, we are left with treating people with established chronic infection in hopes of altering the natural history of their disease. Unfortunately, therapeutic options to date have been disappointing. Interferon alpha (IFNα) was the first drug shown to induce a sustained virologic response and cause an improvement in liver histology. However, IFNα monotherapy is limited by expense, side-effects and poor efficacy. More promising is the combination of IFNα and ribavirin, which has recently become the standard of care for the treatment of chronic HCV. Despite improved response rates, over one half of patients will not respond to this combination. It is apparent that new therapeutic strategies are desperately needed in our battle against HCV. This article will review the currently available therapeutic options for HCV and will explore potential new therapies on the horizon.

Interferon therapy

Interferons are naturally occurring substances that have antiviral and immune modulating effects. Interferon alpha (IFNα) was first shown to have activity against non-A, non-B and post-transfusion hepatitis, before it was discovered that HCV was the major cause of these entities. IFNα has been shown to induce improvement in serum biochemical tests (ALT) and liver histology and to result in the loss of HCV-RNA in some patients with HCV. In 1994, the first Canadian hepatitis consensus statement recommended that patients chronically infected with HCV who had an ALT twice the upper limit of normal (2X ULN) should be treated with a 6-month course of IFNα. Subsequently, it became apparent that the response rate for IFNα therapy depended on duration of treatment, and by 1997 consensus statements in Canada and the United States (National Institutes of Health) recommended treatment with IFNα 3 million units (MU) three times weekly (tiw) for 12 months.[2,3] If patients had not normalized their ALT or the HCV-RNA remained positive after 8-12 weeks, it was recommended that therapy be discontinued because such patients would be unlikely to respond to continued treatment.

Although different dosing regimens and duration of therapy have been investigated, the overall response rates to IFNα monotherapy have been disappointing. Only 10-20% of patients treated with standard IFNα therapy will have a sustained response (disappearance of virus by PCR testing 6 months after stopping therapy).[4] Most patients treated with interferon monotherapy will not clear the virus during treatment (nonresponders), or will only have temporary viral suppression while on treatment, only to show viral relapse after drug cessation (relapsers). In fact, a recent meta-analysis of IFN α2b trials found a sustained response in only 8% of patients.[5] The response to IFNα can be predicted by both viral and host factors.[6] Virological factors such as a low pretreatment serum HCV-RNA level and HCV genotypes other than type 1 result in improved response rates to IFN therapy.[7,8] Patients with established cirrhosis and those with coexisting immunosuppression, including HIV, have lower response rates to IFNα.[9] However, if patients do respond to IFNα therapy the response appears to be durable. In a study of 80 French patients followed for up to 7.6 years after successful IFNα monotherapy, 96% had a sustained virologic response and histologic improvement was noted in 94%.[10] Furthermore, HCV-RNA could not be identified in the liver tissue of any responders. Other studies have confirmed the durability of virologic remission,[11] and it appears that a "cure" of this chronic viral infection is possible.

Despite the overall poor response rates and expense of IFNα monotherapy, it has still been shown to be a cost-effective man-

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agement. Decision analysis modelling has shown that a 6-month course of IFNα monotherapy for histologically mild chronic hepatitis C increases life expectancy with a marginal cost-effectiveness within the acceptable range for medical interventions.[12] Kim and colleagues compared the cost-effectiveness of 6 and 12 months of therapy with IFNα.[13] Although 12 months of therapy is more effective, the marginal cost-effectiveness is slightly more than for 6 months of therapy ($5,000 versus $4,000 US per quality-adjusted life-year gained). They concluded that the costs of IFN therapy are justified, especially in patients under the age of sixty. Interferon therapy also may improve health-related quality of life in hepatitis C patients,[14] and may have long-term benefits in reducing the risks of progression to cirrhosis and development of hepatocellular carcinoma.[15-17]

Other therapeutic trials

The disappointing response rates to IFNα monotherapy have led to the investigation of other agents alone or in combination with IFNα. Other interferons that have been investigated included IFN β and consensus interferon (CIFN), a bioengineered interferon.[18-20] Nonsteroidal anti-inflammatory drugs when given with IFNα do not improve the response rate compared to IFNα alone.[21-23] Small studies have shown some benefit to adding ofloxacin to IFNα.[24,25] The bile acids ursodeoxycholic acid and tauroursodeoxycholic acid improve liver enzymes in HCV patients without impacting on HCV viral levels.[26,27] Herbal and traditional Chinese medicines are being used by many patients, however randomized controlled trials of such agents are limited.[28,29]

Interferon has been combined with the immunomodulatory peptide thymosin with some increase in response rates.[30,31] Trials of the antiviral drugs amantidine and rimantidine have demonstrated limited value.[32-34] Ribavirin is a nucleoside analog with *in vitro* activity against many viruses. Ribavirin monotherapy only causes a transient response in liver biochemistry,[35] however the combination of ribavirin and interferon has proven superior to all other treatments tried to date.
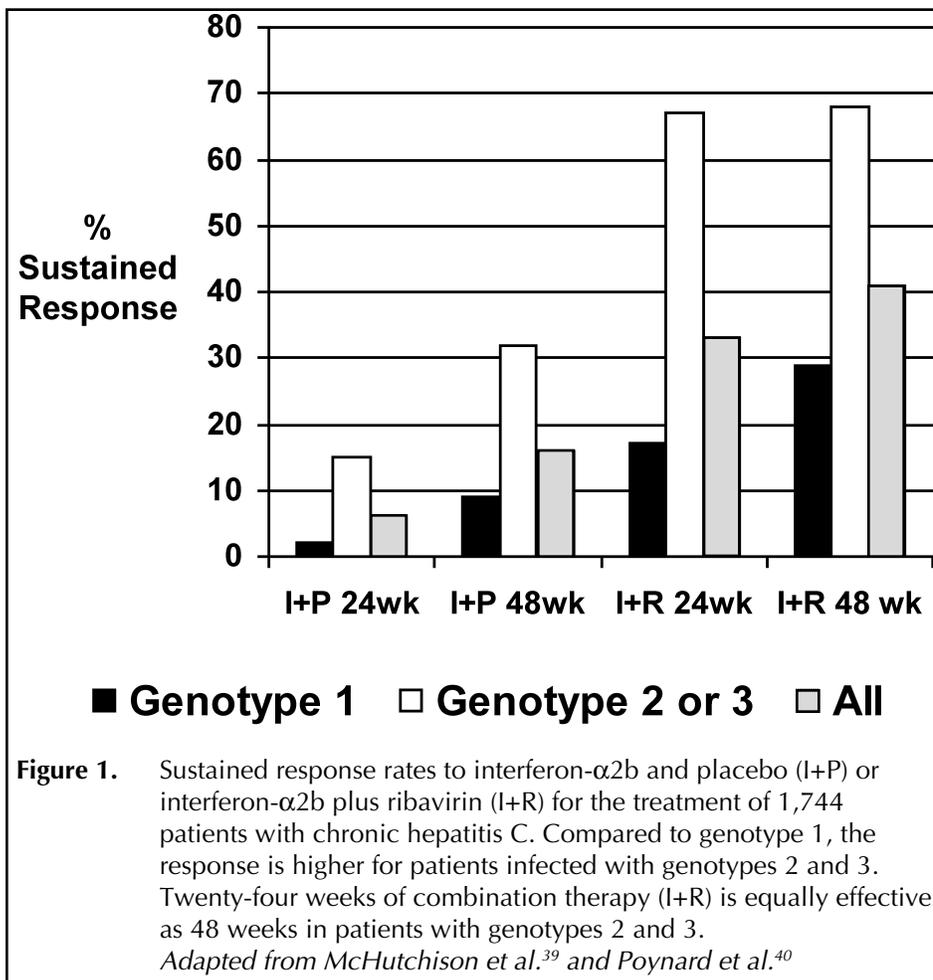
Interferon and ribavirin combination therapy

Three small trials of IFNα and ribavirin therapy from Europe in the mid 1990s showed encouraging results with sustained response rates of approximately 40%.[36-38] Therefore, two large multicenter randomized double-blind placebo-controlled trials of combination therapy were undertaken, one in the USA and one international (including patients from Canada).[39,40] The design of the two trials was similar with patients receiving IFNα + ribavirin or IFNα + placebo for either 24 or 48 weeks (the international trial did not have a 24-week IFNα + placebo arm because 48 weeks of IFNα alone was considered standard of care). Pooling the results of the two trials represents data from 1,744 treatment-naive patients (had not previously received IFNα monotherapy). These results are summarized in Figure 1. The sustained response rate was significantly higher with IFNα and ribavirin being 44% (48 weeks) and 36% (24 weeks) for combination therapy versus 24% (48 weeks) and 11% (24 weeks) for IFNα alone. The response to therapy was influenced by the genotype of the virus. The sustained response to combination therapy was 17% (24 weeks) and 29% (48 weeks) for genotype 1, compared to 67% (24 weeks) and 65% (48 weeks) for genotype 2 (Figure 1). Sustained response was also associated with low viral load, limited fibrosis, female sex and age younger than 40. Combination therapy improves health-related quality of life,[41] and although combination therapy is more expensive it has been shown to be cost-effective.[42]

Other studies have demonstrated that interferon and ribavirin combination therapy is a treatment option for patients who were nonresponders or relapsers following IFNα monotherapy. In a trial of 345 relapsers, 24 weeks of combination therapy resulted in a 49% sustained response compared to 5% in the IFNα monotherapy group.[43] Histologic improvement was also more common in the combination therapy group. Similar results have been found in treating relapsers with consensus interferon (CIFN), with a sustained response rate of 58% after 48 weeks of CIFN.[44]

Based on these results, in 1999 the third Canadian consensus conference on the management of viral hepatitis concluded that the new standard treatment for HCV patients should be interferon 3 million units sc tiw in combination with ribavirin (1000mg if <75kg body weight and 1200mg if >75kg) po daily. The therapy is to be offered to HCV-infected persons with abnormal ALT level (1.5 X ULN) on three occasions over more than three months. A liver biopsy is recommended for grading and staging of disease before initiating therapy. Duration of therapy is determined by the genotype of the virus, with patients carrying type 2 or 3 being treated for 24 weeks and those with type 1 being treated for 48 weeks. In the era of combination therapy, the rule of stopping therapy if the HCV-RNA remains positive at 12 weeks has been questioned, and some recommend checking the PCR at 24 weeks.[45] In a review of 1,010 patients on combination therapy, 7.3% of patients with positive HCV-RNA at 12 weeks ultimately became sustained responders, compared to 2.7% of those PCR positive at 24 weeks.[45] This means stopping treatment at 12 weeks in PCR-positive patients would have missed a sustained response in only 24 of 1,010 patients (2.4%). Although a formal cost-effectiveness analysis has not been done, it is the practice of the authors to treat patients for 16 to 20 weeks and then stop treatment if the HCV-RNA is positive by PCR. If the PCR is negative, we genotype the virus (from a pretreatment stored sample) to determine if therapy is to be stopped at 24 weeks (genotype 2 or 3) or at 48 weeks (genotype 1).

The addition of ribavirin to IFNα increases the side-effect profile and ribavirin predictably causes hemolysis. Monitoring includes a weekly CBC for the first month and then monthly thereafter. The dose of ribavirin should be reduced if the hemoglobin falls below 100 g/L. The TSH should be monitored every 3 months, as there is a risk of thyroiditis with interferon therapy. It is essential to consider the risks and benefits in each patient before initiating combination therapy. Absolute contraindications to combination therapy include decompensated liver disease, active alcohol or substance abuse, and pregnancy or inability to practice adequate contraception, as ribavirin is teratogenic.

Figure 1. Sustained response rates to interferon-α2b and placebo (I+P) or interferon-α2b plus ribavirin (I+R) for the treatment of 1,744 patients with chronic hepatitis C. Compared to genotype 1, the response is higher for patients infected with genotypes 2 and 3. Twenty-four weeks of combination therapy (I+R) is equally effective as 48 weeks in patients with genotypes 2 and 3.
Adapted from McHutchison et al.[39] and Poynard et al.[40]

Future directions

Future treatment options can be conveniently divided into "near-future" and "needs development" categories. In the former, we can discuss drugs and treatment options that have already been developed and in some cases, subjected to phase III clinical trials, but have not yet become licensed or accepted for routine clinical use. In this category are the newer α-interferons that have a polyethylene glycol moiety attached ("pegylated"). Currently there are 2 forms under study: a 40 kDa branched PEG-α2a interferon (Pegasys®), and a 12 kDa linear PEG-α2b interferon (Peg-Intron®). It is clear that pegylation dramatically increases the circulating half-life of interferons from a mean of 9 hours with α2a-IFN to 77 hours with PEG-IFN α2a.[46] Such an increase would lead to a more stable and consistently high level of IFN, and would therefore be expected to improve the antiviral response rates. Indeed, preliminary studies with PEG-α2a suggest that a dose of 180μg sc once weekly induces approximately the same sustained response rates (36%) as combination IFN-ribavirin treatment.[47] Larger randomized trials are underway with both pegylated interferons combined with ribavirin to determine if the PEG-IFN and ribavirin combinations can increase the sustained response rates to 50% or greater.

Other methods of administering standard IFN continue to draw interest and show promising results, but are not yet widely accepted for routine use. In Japan, physicians routinely use high-dose daily induction IFN regimens, typically consisting of 5-6 million units of α-IFN daily for the first month of therapy.[48] In the west, we had always assumed that the higher sustained response rates reported by our Japanese colleagues were due to differences in genotype distributions, however response rates in Japan appear higher in each genotype. The emergence of pegylated interferons will soon make high-dose daily induction obsolete since pegylation produces a similar or higher consistent IFN blood level.

Despite the failure of amantidine monotherapy in HCV patients, a pilot study of Italian patients has recently reported promising results using triple therapy with IFN, ribavirin and amantadine in a small number of nonresponder patients.[49] In this study, triple therapy was associated with a sustained response in 3 of 10 nonresponders to IFN monotherapy. Previous studies in IFN nonresponders treated with other modalities such as CIFN or combination IFN-ribavirin showed discouraging results, with sustained responses of approximately 10%.[44,50] Consequently the exciting results of this pilot study need to be confirmed with a larger controlled trial.

How best to manage this population of nonresponders continues to be a difficult, unresolved issue. The recommendations from the 1999 Canadian consensus conference suggest that nonresponders to IFNα monotherapy be tried on combination IFNα-ribavirin or CIFN. However, virological response rates tend to be discouragingly low. Another way of approaching this problem, however, was recently suggested by Shiffman and colleagues who treated nonresponders with prolonged maintenance IFN monotherapy (3 MU tiw) for 30 months.[51] The rationale for this study is that IFN has anti-inflammatory effects that may be independent of its antiviral effect. In this study, histological improvement was noted in those patients maintained on IFN, despite ongoing viremia.[51] While we await the arrival of new drugs in the "needs development" category, maintenance treatment may be considered in those nonresponders whose liver histology shows marked necroinflammatory activity, with some fibrosis, who may develop cirrhosis within the next few years if left untreated.

"Needs development"

Because the genomic and x-ray cystallographic structures of several critical enzymes in HCV replication and assembly have recently been clarified, chemists and drug manufacturers have been fervently trying to synthesize compounds that might block such enzymes.[52] These enzymes include the HCV-RNA helicase, which is responsible for unwinding or unfolding the

RNA helix to allow replication to start, and several serine proteases which are responsible for cleaving larger viral proteins into smaller ones that will then complex with other viral proteins to eventually assemble into the complete virion.

Unfortunately work on such enzymatic inhibitors is hampered by lack of a suitable cell culture or small-animal model of HCV replication. Moreover, although several candidate helicase and protease inhibitors have been developed and tested in animals, concerns about drug toxicity and lack of efficacy continue to be problems. After all, many essential functions in humans such as blood coagulation depend on the action of serine proteases, and any antagonist drugs would have to be highly specific for viral proteases. However, because of the large number of labs and resources being used to study this issue, our opinion is that an effective and nontoxic helicase or protease inhibitor will be developed within the next 3 to 6 years.

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