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Current View

Causes and management of chronic hepatitis C in treatment experienced patients

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SUMMARY

Chronic Hepatitis C is a major public health issue, affecting >2% of the worlds population. Combination treatment with pegylated interferon alfa and ribavirin is successful in achieving long-term viral suppression in about 50% of patients. The ever-growing population of relapsers and non-responders to PEG-IFN + ribavirin poses a difficult clinical problem. We investigate the causes of treatment failure, whether virus-related (HCV genotype, quasispecies diversity and viral load) or host-related (age, sex, race, fibrosis/cirrhosis, obesity and insulin resistance) and review the results of recently published trials on the treatment of relapsers and non-responders to PEG-IFN + ribavirin, focusing on the prognostic value of week 12 HCV-RNA measurements.

Key Words: Hepatitis C Virus, Pegylated(PEG)-interferon + ribavirin treatment, Consensus Interferon, Difficult-to-treat, Relapsers, Non-Responders

INTRODUCTION

Hepatitis C virus (HCV) infection is a significant public health issue, affecting an ever growing population and leading to serious complications, such as cirrhosis, hepatocellular cancer (HCC) and liver failure. The World Health Organization estimated the world-wide prevalence of the infection in 1999 at 170 million people (>2% of the world's population) and the incidence at 3-4 million new infections per year.[1] Complications of HCV infection cause 8000-10000 deaths per year in the US and are the leading cause for liver transplantation in both US and Europe.[2,3] It is estimated that 1 out of every 4 people infected will develop cirrhosis, half of whom will eventually die from its complications.[4] Estimates based on current prevalence, incidence and natural history predict an escalation of HCV morbidity, mortality and cost of treatment in the coming 2 decades.[5]

The significant clinical and social consequences of HCV infection render the need for prevention and control of the disease imperative. Public education on the modes of transmission, strict control in medical procedures such as transfusions and transplantations and interventions in high risk groups (such as syringe hand-outs to illicit IV drug addicts) have limited the spreading of the infection in the developed world. Furthermore, current treatment strategies achieve prevention of chronic hepatitis C (CHC) in the vast majority of patients with acute infection whenever it is detected and cure CHC in about half of patients with compensated HCV liver disease.[5]

Treatment of Chronic Hepatitis C

The aim of treatment in CHC is to achieve sustained viral response (SVR), defined as non-detectable HCV-RNA for at least 6 months post treatment.[5,6] Monotherapy with classic interferon (IFN) achieved SVR in 6-12% of patients, combination therapy with IFN + ribavirin raised the SVR rate to 38-42%, while current regiments of pegylated interferon (PEG-IFN) α-2a or α-2b + ribavirin achieve SVR in half of patients with HCV genotype 1 and 80% of patients with genotypes 2 or 3.[6-10] The fact that combination of PEG-IFN + ribavirin is superior to classic IFN or PEG-IFN monotherapy and that there is no place for ribavirin monotherapy is undisputed.

Two treatment regimens with comparable efficacy in terms of SVR rates are approved for CHC. Recommen-

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dations stand for the combination of ribavirin with either PEG-IFN α-2a 180μg/wk or PEG-IFN α-2b 1.5μg/Kg/wk. Randomized studies have shown that these regimens achieve SVR in 54-56% of patients with genotype 1 and 76-84% of patients with genotypes 2 or 3.[7,8] Results from a large randomized double-blind study by Hadziyannis et al introduced the recommendation for 48 weeks of treatment at higher ribavirin dose (1000 or 1200mg for patients <75 or ≥75 kg respectfully) for genotype 1 and 24 weeks of treatment with 800mg of ribavirin for genotypes 2 and 3.[11] Data on genotypes 4,5 and 6 are lacking, but patients are treated as for genotype 1. Comparison of the two PEG-IFN formulations in terms of SVR has been attempted in two recent studies. In a prospective, open label, non-randomized study, Escudero et al compared 91 patients treated with PEG-IFN α-2a 180μg/wk + weight based ribavirin to 92 patients treated with PEG-IFN α-2b 1.5μg/Kg/wk + weight based ribavirin and found no significant difference in SVR (65.9% Vs 62% respectively, p= 0.64).[12] In another open label, randomized study reported in AASLD 2008, Rumi et al found that SVR rate was significantly higher in a group of 212 patients treated with PEG-IFN α-2a 180μg/wk + weight based ribavirin, versus 219 patients treated with PEG-IFN α-2b 1.5μg/Kg/wk + weight based ribavirin (66% Vs 54%, p=0.02).[13] Treatment related serious adverse events, drop-out rates for side effects, neutropenia, thrombocytopenia and anemia were similar in the two groups.

Significant progress has been made over the last few years, however about 50% of CHC patients still do not respond to treatment or relapse and will thus not achieve SVR. Furthermore, many patients will experience side-effects leading to dose reduction or discontinuation of treatment. Any reduction in treatment dose (either PEG-IFN or Ribavirin) compromises efficacy and patients should be kept as close to the full dose as possible. As more patients are subjected to newer combination treatments the clinical problem of relapsers and non responders is expected to affect an ever growing population.

Causes of CHC treatment failure

A) Virus-related factors

HCV genotype is a known factor determining response to treatment. Many studies have documented a negative relationship between genotype 1 and SVR. In one study with PEG-IFN + ribavirin, SVR was achieved by 42% of patients with HCV genotype 1, compared to 76% of patients with HCV genotype other than 1 (p=0.0127).[14] Data on genotypes 4, 5 and 6 are relatively scarce and available from limited studies in Egypt and Asia where PEG-IFN + ribavirin achieved SVR in 58% and 57% of patients with genotypes 4 and 5 respectively, while classic IFN + ribavirin achieved SVR in 63% of patients with genotype 6.[15-17]

Apart from HCV genotype, quasispecies diversity is another factor affecting response to treatment. Patients with limited quasispecies diversity are expected to respond more favorably to treatment.[18,19] It is assumed that the rise of interferon resistant HCV phenotypes is more probable in patients with high quasispecies diversity.[20]

Viral load is another determinant of the likelihood of SVR achievement, that has been incorporated into clinical practice as a result of the progress made in PCR analysis. High viral load is a negative prognostic factor for treatment response and SVR.[21,22] The threshold of "high viral load" is set at 600000 IU/ml or 800000IU/ml, depending on the analyzer used to determine HCV-RNA.[23]

B) Host-Related Factors

Age is a factor affecting response to treatment. In older patients (>65 years) immunologic suppression, concomitant disease and drug use decrease response to treatment and increase the rate and intensity of side-effects. Few studies provide data on this age group. In one study, 84 patients aged >65 with genotype other than 1b and without high viral load were subjected to IFN monotherapy. SVR was achieved by 36% while 13% had to terminate treatment due to side-effects.[24] On the contrary, in the pediatric population IFN based therapies have comparable results to adults aged <65.[25] With respect to sex, women tend to have higher rates of SVR but no randomized studies provide confirmation.[26] Race is another factor affecting treatment outcomes with African-Americans responding worse than whites despite no difference in the rates of premature treatment termination or dose reduction between the two ethnic groups.[27] The higher incidence of genotype 1 HCV infections in the former does not fully explain the difference in outcome. Latin-Americans appear to have better response to treatment than African-Americans but worse than other whites.[28]

The presence of fibrosis or cirrhosis is a negative prognostic factor for SVR, but some patients with high grade fibrosis or even compensated cirrhosis can achieve SVR.[29] A major cause for treatment inefficacy in high grade fibrosis or compensated cirrhosis is the frequency and severity of side-effects that often lead to treatment discontinuation.[30,31] Moreover, high grade fibrosis, cirrhosis and thrombocytopenia are independent prognostic factors of treatment failure.[32,33]

Obesity and liver steatosis reduce treatment efficacy. Hepatic steatosis has been shown to affect HCV kinetics, decreasing early viral load drop during treatment and increasing the possibility of relapse after the completion of treatment.[34,35] Weight loss must be an important part of the approach to CHC treatment, especially in patients about to be retreated. Furthermore, insulin resistance appears to be an independent negative prognostic factor for SVR following treatment.[36,37]

In concluding host-related factors affecting treatment outcomes, some mention must be made to certain special patient groups.

Transplanted Patients

CHC is the most common cause of liver transplantation.[2,3] The transplanted liver is infected by HCV and, owing to immunosuppressive treatment, some patients will present rapidly progressing hepatitis.[15] Ideally, treatment of HCV prior to transplantation is desirable but unfortunately is usually unfeasible as most patients have decompensated cirrhosis. Post-transplantation combination treatment with PEG-IFN + ribavirin achieves SVR in 20% of patients, but many cannot tolerate it.[6] The decision for treatment following transplantation must be made on a case by case basis and should be undertaken by teams of physicians familiar with both CHC and liver transplantation, taking into account both risks and expected benefit for the patient.[5]

HIV-HCV Co-infection

Twenty-five to thirty per cent of HIV positive patients are expected to be infected also by HCV.[38] In these patients the progression of CHC to end stage liver disease is about twice as fast.[39] Slightly lower SVR rates are reached by combination therapy with PEG-IFN + ribavirin in HIV infected patients.[40] In patients with CD_4 count <200 cells/mm^3 control of the immunodeficiency syndrome using Highly Active AntiRetroviral Therapy (HAART) is the primary concern and CHC should be treated after stabilization of the HIV infection.[41]

Illicit Drug / Alcohol Users

Patients who have stopped using drugs or alcohol do not differ from other CHC patients. Patients on methadone and active drug users, provided they are on some program of treatment and surveillance, can occasionally be candidates for CHC treatment with comparable results to other CHC patients if compliance is preserved.[5]

Abstinence from alcohol should be recommended to all patients undergoing treatment for CHC. Safe levels of alcohol consumption have not been determined.[42] Therapy in alcoholics should also be targeted to treatment of the addiction.[5]

The main factor limiting treatment efficacy in drug and/or alcohol users is poor compliance. Psychiatric comorbidity can further adversely influence compliance and cause premature treatment termination.[43,44]

Management of Non-Responders and Relapsers

Modern-day treatment regimens achieve SVR in slightly more than half the patients with CHC. However, a significant number of patients does not respond or relapse following treatment. As more patients with HCV infection are subjected to treatment, the population of these difficult to treat patients is expected to rise, resulting in the emergence of a difficult clinical problem.

Treatment options suggested for these patients include retreatment with a more potent antiviral regimen, dose and/or treatment duration increase and long-term "maintenance" treatment with low dose PEG-IFN. The natural history of CHC must be taken into account in our therapeutic decisions, since patients with minimal or no fibrosis on liver biopsy have a low probability of progression to decompensated liver disease and may not need to be subjected to long-lasting and cumbersome treatments.

Patients who initially responded to antiviral treatment but eventually relapsed are expected to respond again in a new cycle of treatment. SVR can be achieved in as much as 40-50% of patients, if a more potent antiviral regimen is used. PEG-IFN + ribavirin combination treatment is indicated in patients who relapsed after one of the older treatment regimens and should be attempted in such cases.[5]

Management of relapsers and non-responders to PEG-INF + ribavirin combination treatment is much more challenging. The EPIC trial, sponsored by Schering-Plough®, manufacturer of PEG-IFN α2-b, achieved SVR in 16% of 299 patients who had relapsed or did not respond to previous PEG-IFN + ribavirin treatment, using PEG-IFN α2-b 1.5μg/Kg /wk + ribavirin 800-1400 mg.[45] In the subgroup of non-responders (n=172) SVR rate was 4% and in the subgroup of relapsers (n=112) 36%. In the entire study population, which also included patients who had failed other (non-pegylated) IFN-based treatments, positive predictive factors for SVR were relapsers, non-responders with HCV genotype 2 or 3, low viral load, low grade of fibrosis pre treatment and the absence of detectable HCV-RNA at week 12 of treatment (also known as complete early viral response – cEVR). However, only 12% of patients

who had >2log decrease but still detectable HCV-RNA at week 12 achieved SVR. Most of these patients had undetectable HCV-RNA by week 24. The REPEAT trial sponsored by Roche® achieved 16% SVR in 473 non-responders to previous PEG-IFN α2-b + ribavirin therapy, using PEG-IFN α2-a 180μg/wk + ribavirin 1000-1200mg for 72 weeks, with or without an induction phase of PEG-IFN α2-a 360μg/wk for the first 12 weeks.[46] In the same study, a second group of non-responders (n=472) were treated for 48 weeks, with or without the induction phase, and 8% achieved SVR. Statistical analysis showed no benefit from the induction phase with PEG-IFN α2-a 360μg/wk but did prove benefit from prolonged 72 week therapy. As in the EPIC study, advanced fibrosis was a negative prognostic factor for SVR and cEVR a positive one, with 57% of patients who had cEVR eventually achieving SVR, versus 4% in patients with detectable HCV-RNA at week 12. Direct comparison of the two trials is difficult since they differ in both treated population (relapsers and non-responders to PEG-IFN + ribavirin Vs non-responders to PEG-IFN α-2b + ribavirin) and duration of treatment (48 Vs 72 weeks, with or without induction phase). However, both studies stress the importance of cEVR as an early prognostic factor and give some hope of treatment in these difficult-to-treat patients. Based on these two trials, regulatory authorities in the USA and EU have approved the indication to treat non-responders and relapsers for 48 weeks with PEG-IFN α-2b + ribavirin or 72 weeks with PEG-IFN α-2a + ribavirin.

A recent study by Scotto et al directly compared the efficacy of the two PEG-IFN formulations in 108 patients who had previously not responded to IFN-a + ribavirin for >3 months.[47] In this study, PEG-IFN α-2a 180μg + ribavirin 15mg/kg achieved SVR in 11 (20.8%) of 54 patients, while PEG-IFN α-2b 1.5μg/kg + ribavirin 15mg/kg in 10 (18.4%) of 54 patients.

Consensus interferon (CIFN) has also been tried in this group of patients with encouraging results. CIFN is a genetically modified molecule developed by assigning the most commonly observed amino acids of natural interferon – alpha subtypes to produce a novel "consensus" interferon. CIFN has demonstrated higher biologic activity than natural IFN.[48] Compared with INF α-2a and INF α-2b, CIFN exhibits higher antiviral, antiproliferation and natural killer cell activation activity.[48] In a recent retrospective study of 137 non-responders to PEG-INF α-2b + ribavirin who were treated with CIFN + weight based ribavirin, the rate of SVR was 37%.[49] Patients were given daily doses of 15μg/kg of CIFN for the first 12 weeks and responders were then given the same dose 3 times / week. In studies of non-responders and relapsers to older treatments, reported SVR rates with CIFN were 26-30% for the former and up to 56% for the latter.[50-52] A phase 3 trial of CIFN was recently completed and published.[53] CIFN 9 or 15 μg/day plus weight based ribavirin (1000-1200) was used in 487 non responders to previous PEG-IFN based treatments. SVR rates were 6.9% and 10.7% in the 9 and 15 μg/day groups respectively (p=ns). Thirteen of 16 patients in the 9 μg/day group and 14 of 22 in the 15 μg/day group who achieved cEVR went on to demonstrate SVR. Patients deemed "slow responders" (>2log drop at week 12, HCV-RNA negative at week 24) achieved SVR rates of 11.7% and 35.4% in the 9 and 15 μg/day groups respectively. Finally, only two patients in each group achieved SVR despite being HCV-RNA positive at week 24.[53]

All the aforementioned studies despite their differences in drugs used, doses and duration agree that HCV-RNA at week 12 is a paramount prognostic factor. Patients with cEVR have reasonable SVR rates and should continue treatment. Slow responders (>2log drop at week 12, HCV-RNA negative at week 24) may also achieve SVR, in much lower rates though, and more studies are needed to determine whether they should continue treatment. All other patients are highly unlikely to achieve SVR and therefore should not continue treatment.

Long-term treatment with a reduced dose of IFN in patients who failed to achieve SVR in order to prevent disease progression has been evaluated in a few small studies that showed that this strategy can maintain biochemical and virological response and can prevent liver histological progression in patients with an initial response to IFN therapy.[54,55] Three large multicentre trials (HALT-C, COPILOT, EPIC3) are evaluating the safety and efficacy of reduced dose PEG-IFN maintenance treatment in CHC patients with advanced fibrosis or cirrhosis who did not reach SVR after the initial treatment. The HALT-C trial did not show any benefit on clinical disease progression from prolonged (3,5years) treatment with PEG-IFN α-2a 90μg/wk, despite the fact that ALT levels, necro-inflammatory scores and HCV-RNA were significantly reduced in the treatment group.[56] Furthermore, 17% of patients had to terminate treatment by year 1.5 and 30% by year 3.5 due to side-effects, while only 59% of patients were able to maintain the starting dose of PEG-IFN for the full 3.5 years. In contrast to previous small studies, no reduction in the incidence of hepatocellular carcinoma was documented in the treatment group. The authors concluded that prolonged treatment with half-dose PEG-IFN is ineffective and should not be indicated in patients with HCV-associated advanced fibrosis (with or without

cirrhosis) who did not respond to previous standard dose of PEG-IFN + ribavirin.[56]

Because of the escalating importance of the clinical problems posed by relapsers and non-responders, a number of new compounds are being investigated. New interferon formulations, ribavirin analogues, immunomodulators, and anti-fibrotic agents provide hope for the future. Drugs targeting specific proteins of HCV (Specifically Targeted Antiviral Therapy for HCV – STAT-C) are being studied and some have entered tolerability, safety and effectiveness trials.[57] Due to issues of viral resistance, some of these agents are tested in combination with IFN.

Conclusions

Over the last few years important steps have been made in the treatment of CHC and, as a result, about half the patients clear the virus after a single cycle of treatment. However, an ever-growing number of patients who relapse or do not respond to treatment pose a significant clinical problem. Many factors can lead to treatment failure, unfortunately most of which are unmodifiable. Treatment regimens with PEG-IFN or possibly CIFN plus ribavirin can help some of these patients clear HCV. In patients undergoing retreatment, cEVR (HCV-RNA negative at week 12) is an important positive prognostic factor for SVR. Patients with detectable HCV-RNA at week 12 with >2log decline may only continue treatment if it becomes undetectable by week 24. Long-term low- dose PEG-IFN treatment is ineffective and not indicated. Research into new drugs can provide more treatment options in the future.

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