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REVIEW

Treatment of hepatitis C virus infection

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Abstract

Acute and chronic hepatitis C virus (HCV) infection remains a serious health problem worldwide, however, there has been advancement in the treatment of HCV infection due to standard treatment using pegylated interferon and ribavirin. The literature indicates that therapy for HCV is becoming more individualized. In addition to considering genotype and viral RNA levels before treatment, achievement of an early virologic response (EVR) and a rapid virologic response (RVR) is now possible during therapy. Moreover, problem patients, such as non-responders, relapsers, HIV or HBV co-infected patients, patients with liver cirrhosis, and pre- or post-liver transplantation patients are an increasing fraction of the patients requiring treatment. This article reviews the literature regarding standard treatments and problem patients with acute and chronic HCV infection. It also includes discussion on contraindications and side effects of treatment with interferon and ribavirin, as well as new drug development.

Key words: Hepatitis C virus; Acute and chronic HCV infection; Treatment; Pegylated interferon; Ribavirin; Sustained virologic response; Non-responders; Relapsers

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INTRODUCTION

Infection with hepatitis C virus (HCV) remains a severe life-threatening medical and public health problem worldwide. Every year there are an estimated 3 to 4 million new cases of infection due to transfusion contamination, contaminated injection needles, and parenteral exposure[1-5]. There is a lower rate of infection for sexual transmission[6]. About 55%-85% of individuals with acute HCV infection become chronically infected and are at risk for developing hepatocellular injury, liver cirrhosis, hepatocellular carcinoma or liver failure[7-9].

In total, More than 170 million individuals (> 2% of the world's population) are infected with HCV[10]. While prevention of primary infection is possible, vertical transmission of HCV remains a significant problem especially in developing countries.

The transition from acute to chronic infection is only partly understood. However, early treatment with pegylated interferon (PEG-IFN) alpha to prevent chronic infection is effective in up to 95% of patients with acute hepatitis[11-13]. Determining the optimal treatment for chronically infected individuals is a remaining question. To date, standard treatment for chronically infected patients is the combination of PEG-IFN alpha with ribavirin[14]. Recent studies have demonstrated that a relatively high number of patients acquire sustained virologic response (SVR), defined as non-detectable serum virus RNA levels by qualitative PCR 6 mo after end of treatment[15,16], and this is the primary goal of therapy. However, a large number of patients remain viraemic and chronically infected. In addition, many patients suffer from severe side effects while receiving this combination therapy[14-17]. These are the reasons for attempts to find medications with higher SVRs, better tolerability and shorter treatment regimens[18-21]. Moreover, alternative therapeutic regimens, such as an effective therapeutic or prophylactic vaccine for HCV infection, are being sought after and developed[22-26].

TREATMENT OF ACUTE HEPATITIS C

Diagnosis of acute HCV infection is a rare event since acutely infected individuals are mostly asymptomatic[27,28]. Also, social problems within high risk groups (especially injection drug users) keep these individuals from seeing physicians.

An optimal treatment for acute HCV infections has not been established. There are several studies showing excellent responses using IFNα[11]. The best results, with a SVR in over 95% of the patients, were achieved by using 5 million international units (MIU) of IFN daily for 4 wk, followed by 5 MIU three times weekly for another 20 wk. This treatment was well tolerated in most cases. Another recent study achieved a SVR in 87% of patients, using 6 MIU of IFN injected intramuscularly daily for 4 wk[29]. In acute HCV, genotype and RNA serum levels seem to have no influence on treatment outcomes[11,30]. While undergoing treatment, patients need to be monitored at

least every four weeks for transaminases, HCV antibodies and serum RNA levels.

Since spontaneous viral clearance is documented in up to 50% of acutely infected individuals[13,30-32], some authors believe treatment should be initiated after three to four months of observation. The data to date show a worse outcome following this policy[11,13], but patients avoid the potential severe side effects of IFN therapy[33]. Also, this scheme gives an opportunity for patients with contraindications to IFN therapy; i.e. pregnancy, acute alcohol or i.v. drug abuse, and psychiatric diseases such as severe depression, to resolve these problems before starting therapy[14,17,34]. Nevertheless, delaying therapy for acute HCV infection beyond three months after onset of the disease cannot be recommended since one study showed this resulted in a dramatic drop of SVR rates (from 87% to 53%)[29]. Even if IFN monotherapy is sufficient for the therapy of acute HCV infection[35], preliminary data suggest PEG-IFN to be as effective as the IFN regime used in the reported German trial[35]. Recently, Wiegand *et al*[12] published a trial using PEG-IFN alpha-2b 1.5 μg per kg body weight with patients that had acute HCV infection. In patients adherent to therapy, a SVR of 94% after therapy and 89% after a follow up of 24 wk was achieved. In non-adherent patients (less than 80% of PEG-IFN application in 80% of scheduled treatment duration), the rates dropped to 82% and 71%, respectively. Furthermore, Kamal *et al*[36] presented a study demonstrating a combination therapy of PEG-IFN and ribavirin to be more effective than PEG-IFN monotherapy (increase of SVR from 80% with monotherapy to 85% with combination therapy). In addition, it was shown that the time point to start treatment after onset of disease is very important. A recent trial demonstrated that overall SVR dropped from 95% to 92% and then to 76% when treatment was started 8, 12 or 20 wk after onset of disease[37], respectively. Considering these data, we suggest treating acute HCV infection for 24 wk, starting immediately or at three months after onset of the disease, using a combination of PEG-INF and ribavirin in a dosage recommended for treatment of chronic HCV infection (see below).

TREATMENT OF CHRONIC HEPATITIS C

The primary treatment goal for chronic HCV infection is, as mentioned previously, sustained virologic response (SVR)[38,39]. With the recommended treatment, SVR can be achieved in about 55% of patients who are chronically infected with genotype 1 of HCV, while with genotype 2 and 3 the efficacy is 80% or greater[15,16,40]. The standard therapy is PEG-IFN alpha-2a or PEG-IFN alpha-2b subcutaneously in combination with twice daily oral doses of ribavirin[15,16,41]. The combination has proven to be more efficient than monotherapy alone, even though the antiviral mechanism of ribavirin is not fully understood[42]. Ribavirin monotherapy has no therapeutic effect in HCV infected patients[43,44].

There are two widely accepted regimens that can be followed, with both showing comparable SVR rates. Published in 2001 by Manns *et al*[15], PEG-IFN alpha-2b in a dose of 1.5 μg per kg body weight once a week subcutaneously plus oral ribavirin 800 mg daily led to a virus clearance of 54%. Higher ribavirin doses resulted in a lower efficacy. While genotype 1 must be treated for 48 wk to achieve the best results, treatment longer than 24 wk for genotype 2 and 3 did not raise SVR rates beyond 82%. A trial by Fried *et al*[16] using PEG-IFN alpha-2a demonstrated comparable results. Using PEG-IFN alpha-2a in a dose of 180 μg once a week subcutaneously plus 1000-1200 mg (depending on body weight, cut-off 75 kg) of oral ribavirin daily resulted in 56% of SVR in genotype 1 carriers, and 80% in genotype 2 and 3 carriers. Patients with genotype 1 were treated for 48 wk. In patients infected with genotype 2 and 3, a treatment period of 24 wk seemed to be sufficient. Recently, two studies have shown that treatment can be abbreviated in patients with low baseline levels of HCV-RNA (< 600 000 IU/mL) who become HCV-RNA negative. Treatment of genotype 2 and 3 for only 12 or 16 wk may be sufficient for a special population[45,46]. Therefore, therapy for HCV infection is becoming an individualized therapy.

In summary, for patients who are chronically infected with HCV, the recommendation is to use PEG-IFN alpha-2b 1.5 μg/kg per week or PEG-IFN alpha-2a 180 μg/wk plus ribavirin 1000-1200 mg/d (body weight dependent) for 48 wk for patients with genotype 1 or 24 wk for patients with genotype 2 or 3. For genotypes 4, 5 and 6, the data are not sufficient for the development of a guideline, but it has been suggested to treat patients with these genotypes in a similar way as for patients with genotype 1[47,48]. Recently, Hadziyannis *et al*[40] presented a study on 36 genotype 4 carriers. While patients in the short-term group (24 wk) had a SVR of 63%-67%, treatment for 48 wk resulted in a SVR of 82.

Induction therapy does not result in higher SVR rates, therefore a recommendation regarding induction therapy cannot be given[49,50], but there are ongoing individual trials. While it is recommended to treat patients with relapse of HCV or non-responders after IFN alpha monotherapy with the described combination of PEG-IFN and ribavirin[51-54], the treatment indication for non-responders or patients with relapse after treatment with PEG-IFN alpha and ribavirin is controversial. Recent studies do not offer a general recommendation. Controlled trials to answer this question are ongoing.

During therapy, monthly monitoring of side effects, blood count, transaminases, creatinine, urea and glucose should be made. For the first 2 mo of therapy, blood counts should be made every 2 wk. Thyroid function should be considered in 12 wk intervals by measuring thyroid stimulating hormone (TSH). To monitor treatment efficacy, HCV-RNA should be determined quantitatively before and 12 wk after the start of therapy. If the RNA level drops less than 2 logs-known as early virologic response (EVR)-or remains detectable at wk 24, a successful treatment is extremely unlikely and therapy should be stopped[15,16,55-58]. The same is true if after 24 wk HCV-RNA is still measurable[59].

As mentioned above, successful treatment is defined as SVR and undetectable HCV-RNA 6 mo after the end of therapy. A recently described predictive factor is the rapid virologic response (RVR), defined as undetectable

HCV RNA levels at wk 4 after the start of treatment. For patients who have genotype 1 with a low baseline viral load (< 600 000 IU/mL) and who have achieved RVR under therapy with continuous undetectable HCV-RNA afterwards, a treatment course of 24 wk may be required to match comparable results to the standard treatment of 48 wk[60]. For patients with genotype 2 or 3 and a RVR followed by undetectable RNA levels, therapy for 16 or even 12 wk may be sufficient[46]. However, reducing treatment duration in these patient populations remains controversial[61]. Therapy to increase SVR and reduce side-effects for chronic HCV infected patients is becoming more often designed for the individual, with genotype, EVR, RVR and the HCV-RNA level before start of treatment as predictors for achieving a SVR.

TREATMENT OF HEPATITIS C INFECTION IN CHILDREN

Children suffering from chronic HCV infection generally show no symptoms. While biochemistry and histology are comparable to adults with HCV, the progression of hepatitis C seems to be slower compared to adults[62-64]. It has been shown that, in general, children tolerate IFN therapy relatively well. Side effects are usually mild or moderate. One study of 41 children receiving standard combination therapy showed an overall SVR of 61% one year after treatment[65]. Altogether response rates in children to INF monotherapy and combination therapy with INF and ribavirin seem to be equivalent to adults[14,64,66,67], PEG-IFN is not yet approved for use in children. Therefore, the present regime is 15 mg ribavirin per kg body weight per day plus 3 MIU/m^2 body surface interferon alpha-2b three times per week[68]. This treatment appears to be reasonably safe and effective in children with hepatitis C. Prospective controlled trials evaluating combination therapy with PEG-INF are being developed.

SIDE-EFFECTS AND CONTRAINDICATIONS FOR TREATMENT OF HEPATITIS C INFECTION

Should everybody with chronic HCV infection be treated? Patients with signs of hepatitis, such as elevated transaminases (serum alanine aminotransferase level, ALT), and beginning fibrosis in liver biopsy are thought to be the most appropriate group to undergo therapy[14,69]. Nevertheless, patients with normal transaminases have the same outcome as individuals with elevated ALT[70].

People without the necessary motivation and compliance to therapy should be considered as untreated. Costs of treatment and severe side-effects must be weighed against the low efficacy of therapy in this group[14,34,71,72].

There are some absolute and relative medical contraindications for treatment with IFN, PEG-IFN and/or ribavirin. Since ribavirin is teratogenic, in both males and females, anticonception is recommended during therapy and at least 6 mo after end of therapy[73]. Also breast feeding should be avoided. People with cardiac problems rarely develop reversible arrhythmia[74] or cardiomyopathy[75] under interferon therapy. But for patients with significant cardiac disease, death from cardiac failure is more likely than from chronic hepatitis C. Therefore, within this patient group anti-viral therapy can be dispensed.

Further contraindications for treatment with interferon and/or ribavirin are hepatic decompensation and renal failure. Interferon and ribavirin can enhance liver failure[76] and, as mentioned above, close monitoring is required. Some hepatic comorbidities, additional to chronic HCV infection, are discussed later. Ribavirin undergoes renal elimination. Therefore, renal impairment leads to elevated serum levels of ribavirin, enhancing side-effects such as hemolysis. The same is true for INF, while PEG-IFN, due to its molecular size, is better tolerated in patients with end stage renal disease. PEG-IFN alpha-2a does not result in elevated serum levels even with creatinine clearance < 30 mL/min. Since kidney diseases often do not limit life expectancy, antiviral therapy must be considered in patients with both chronic HCV and end-stage renal disorder[77,78]. Available data suggests higher SVR rates in patients with renal disease, using IFN monotherapy, compared to patients with normal renal function[79,80]. Few studies have dealt with very low dose ribavirin application in these patients[81,82], alone or in combination with PEG-INF. PEG-INF α-2a should be reduced from 180 μg to 135 μg, while the recommendation for PEG-INFα-2b is dose reduction by 50%[83].

The immune system is heavily influenced by both ribavirin and interferon and this is the probable mechanism of their antiviral activity. But in HCV patients with comorbid autoimmune disease, both drugs could worsen the disease. Therefore, application of antiviral therapy must be considered dangerous as long as the autoimmune disease is not controlled.

The most common side effects of treatment with PEG-IFN are fatigue, muscle aches and psychological disorders such as depression, irritability, anxiety and sleep disturbance. Interferon further induces pancytopenia through its bone marrow depressing activity[15,16,84]. The most common adverse effect of ribavirin is haemolysis and anaemia. Therefore, patients treated with the combination therapy suffer from anaemia, with the lowest haemoglobin 4 wk after initiation of treatment[84]. Patients with ischaemic problems should be monitored closely and, if necessary, should have blood components transfused. The application of growth factors, such as erythropoetin, G-CSF or GM-CSF, cannot generally be recommended considering the cost-benefit-ratio, but growth factors may be useful in some patient populations. Significantly higher risk for bacterial infection has not been demonstrated during treatment with ribavirin and/or PEG-IFN[15,16,85,86]. The most common autoimmune reaction to therapy is the development of autoimmune thyroiditis[15,16,84,85,87]. Flu symptoms caused by interferon can be treated with paracetamol or similar drugs[84], and thyroid disorders by hormone application. More severe side effects are mood changes and depression[15,16,84,88]. The later is especially true in people already suffering from instable psychiatric

disorders prior to therapy. Mild symptoms can be covered by selective serotonin reuptake inhibitors (SSRI)[89], while development of severe depression or suicidal tendencies are clear indications to discontinue therapy.

Rare side-effects are hearing impairment, hair thinning and loss, insomnia, visual disorders, interstitial pneumonia, pancreatitis, colitis and exacerbation of inflammatory diseases[83,84]. Every patient should be informed sufficiently about potential adverse events before therapy is started.

TREATMENT OF HEPATITIS C IN PATIENTS WITH LIVER CIRRHOSIS

Mortality from hepatitis C is mainly due to manifest cirrhosis. Liver biopsy studies indicate that hepatic fibrosis may regress under therapy with PEG-IFN and ribavirin[90,91]. The recommendation today is to treat patients with compensated cirrhosis with the standard combination therapy[92,93]. While patients with Child-Pugh A and B cirrhosis respond and tolerate this therapy relatively well[15,16,40,87,94], it is unclear whether a drug reduction in Child C cirrhosis should be recommended[95-97]. In general, antiviral therapy in decompensated liver cirrhosis is not recommended[98].

There is data indicating that reduction of body weight in obese patients is associated with reduction in hepatic fat[99,100] and in some cases of fibrosis[101], resulting in a better response to antiviral treatment.

A study carried out on a Japanese population demonstrated the prevention of hepatocellular carcinoma (HCC) in individuals receiving antiviral therapy[102]. The same effect may be found in Caucasians[103,104]. Successful antiviral therapy also reduces the rate of hepatic decompensation.

Overall, even if liver transplantation in end-stage disease is not prevented by antiviral therapy, the data suggest that recurrence of disease after transplantation is significantly lowered if treated previously[76].

TREATMENT OF HEPATITIS C IN PATIENTS AFTER LIVER TRANSPLANTATION

Chronic HCV infection with end-stage liver disease or hepatocellular carcinoma due to HCV is currently the most common indication for liver transplantation[105,106]. All transplanted patients become reinfected with HCV[107-111] and, combined with immune suppressive therapy to avoid rejection of the organ, some patients develop rapid progressive hepatitis[109,112-115]. In addition, acute rejection seems more frequent in patients with liver transplantation for hepatitis C[116,117].

Before transplantation, the patient should be treated for HCV infection, if possible (see above)[96,97,118]. Unfortunately, most patients in need of transplantation have decompensated disease, limiting effective antiviral therapy before transplantation[76]. Even when IFN combined with ribavirin was previously used[119-121], after transplantation the standard treatment should be PEG-IFN and ribavirin[122-128]. Nevertheless, SVR rates post-transplantation were significantly worse compared to antiviral treatment in the non-transplantation setting. Overall, SVR rates post-transplantation are only about 20%[119,123,127,129-131]. Furthermore, in a high percentage of patients, interferon and ribavirin are poorly tolerated after liver transplantation and therapy must be considered carefully[83,131].

TREATMENT OF HEPATITIS C IN PATIENTS CO-INFECTED WITH HIV

There is a high rate of patients co-infected with HCV and HIV due to the same transmission route in high-risk populations. An estimated 25%-30% of patients with HIV are co-infected with HCV in Europe and the United States[132]. In these patients, HCV progression to end-stage liver disease is almost doubled[133,134]. Therefore, it is favourable to treat these patients as early as possible, if they have no other contraindications.

Since therapy for HCV does not significantly increase HIV RNA levels, it is recommended to use standard treatment with PEG-IFN and ribavirin. SVR rates in co-infected patients are slightly lower than in the mono-infected population[135,136]. For genotype 1 (and 4), SVR ranges from 14% to 29%, while for genotype 2 and 3 it ranges from 44% to 73%[137-139]. Patients on antiretroviral therapy are more likely to develop the side-effects of ribavirin[139-141]. These patients must be monitored closely and, in the case of severe side effects, ribavirin should be reduced or discontinued.

If HIV infection itself is not stable (CD4 count < 200 cells/mm), highly active antiretroviral therapy (HAART) should be initiated first and secondarily, after stabilisation, treatment for HCV should be started[142-144].

NEW THERAPEUTIC IDEAS FOR PATIENTS INFECTED WITH HEPATITIS C

Since the number of non-responders or patients with relapse is increasing, many new drugs are being tested briefly. Meta-analysis of several controlled trials for amantadin, for example, showed a significantly better SVR with amantadin and IFN alpha compared to IFN alpha monotherapy[19,20,145]. Further, a German study showed an increase of SVR using a triple therapy of INF alpha plus ribavirin plus amantadin compared to INF alpha plus ribavirin plus placebo[18]. Still missing are trials with PEG-INF, ribavirin and amantadin, as well as studies looking at long-term outcomes.

Further, alternative interferon types and ribavirin analogues, for example viramidine, which is a ribavirin prodrug cleaved to ribavirin in the liver, were tested to reduce side effects and were found to vary in success[146-148]. Most promising are specific inhibitors, such as specific HCV protease and HCV polymerase inhibitors, which were tested in experimental settings or phase 1-2 studies currently[21,26]. In phase 1 and 2 trials, several HCV specific protease inhibitors, such as BILN 2061, VX 950, SCH 503034, demonstrated a reduction of HCV RNA levels from 2 to 4.4 $\log_{10}$ from baseline[149-153]. Due to cardiac toxicity, further development of BILN 2061 has been

stopped. VX 950, which is another protease inhibitor, significantly lowers HCV-RNA levels more than 4 $\log_{10}$ units within the first 14 d[154]. Unfortunately, in the follow-up, the concentration increased again, probably due to mutational resistance. Nevertheless, since RVR is a strong positive predictive factor, a combination of standard therapy together with VX 950 could increase SVR rates. Similar results are true for SCH 503034 with a HCV-RNA drop of 2 to 3 $\log_{10}$ units. Also, specific polymerase inhibitors and nucleosid analogues have been tested for reduction of HCV RNA levels[155,156]. They result in a reduction of HCV-RNA concentrations, but they seem to be less effective in their antiviral activity than protease inhibitors[157]. Studies combining polymerase inhibitors with standard therapy are ongoing and it is most likely that polymerase and protease inhibitors will be combined with PEG-IFN in the future.

Additional concepts are the use of toll-like receptor agonists and RNA-based therapy[26], as well as drugs like thymosin-α, inosinmonophaphatedehydrogenase inhibitors, anti oxidants, glucosidase inhibitors, cytokines, inhibitors of the internal ribosomal entry site (IRES) and fusion proteins. Silymarin, which in some cases resulted in a drop of the transaminases, does not produce an effect on HCV-RNA concentration and liver histology in the trials presented to date. Most eagerly, many approaches involve a search to find a vaccine to prevent HCV infection[24,25,158].

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