Hepatitis C infection: the quest for new treatment strategies
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Chapter 10

Summary
Chapter 10

In this thesis various, on interferon based, treatment schedules for HCV patients are described. It also points out the possibility of serious side effects of treatment.

Chapter 1 (general introduction) summarizes the current knowledge of the hepatitis C virus and gives an overview of therapy development since its introduction.

In chapter 3 the efficacy of 6 and 36 month treatment with interferon-alpha for chronic hepatitis C patients is described. The sustained virological response was 13% after 6 months (standard) and 40% after 36 months (long-term) of treatment. Especially in patients with a virological breakthrough or relapse after standard treatment, long-term (re)-treatment was effective. In patients with a virological non-response during standard treatment, long-term prolonged treatment was not effective. Non-treated control patients showed a stable viral load during the observation period and no spontaneous clearance of HCV.

Chapter 4 shows the results of 6 month standard treatment with interferon/ribavirin combination therapy and interferon monotherapy. Sustained viral response was achieved in 45% patients after interferon/ribavirin therapy and in 10% patients after interferon monotherapy. A 100% negative predictive value for sustained viral response could be established before the start of therapy for patients aged > 40 years and treated with interferon monotherapy. A 100% negative predictive value for sustained viral response was also found for patients treated with interferon monotherapy without a viral load decrease of ≥ log 1 IU/mL at week 2 of treatment. For patients treated with interferon/ribavirin combination therapy this negative predictive value was 97% when there was no viral load decrease of ≥ log 1 IU/mL at week 2 of treatment.

While 15 months on treatment with interferon-alpha/ribavirin combination, a chronic hepatitis C patient develops symptoms of myasthenia gravis, a neuromuscular disorder of autoimmune origin. Development of myasthenia gravis has been reported in 3 patients treated with interferon monotherapy but no cases of myasthenia gravis has been reported in patients treated with the combination therapy. This issue has been exposed in chapter 5.

In chapter 6 high dose interferon induction treatment is evaluated. Thirteen treatment naïve chronic hepatitis C patients received 6 million units of interferon every 8 hours for 2 weeks. Hepatitis C virus RNA levels were determined daily during treatment. Since a 3 log viral load decline early during treatment is an important prognostic factor for sustained virological response, the time interval for a 3 log decline for patients in this study was calculated. In patients infected with genotype non-1, a 3 log decline of viral load was found 2.4 days after start of induction therapy. Only one of three patients infected with genotype 1 had a 3 log decline during treatment. At the end of the 2 week treatment period 54% of patients were hepatitis C virus RNA negative. However, only one patient achieved a sustained virological response. All other virological responders at the end of the treatment had a virological relapse.

The same interferon high dose induction schedule for 2 weeks in combination with ribavirin and amantadine (another broad spectrum anti-viral drug) was the treatment given to virological relapse patients of which the results are been described in chapter 7.
When treatment was continued for 22 weeks with standard interferon in combination with ribavirin and amantadine, 44% achieved a sustained virological response and 29% of the patients with an end of treatment virological response had again a virological relapse. Of all pretreatment characteristics only genotype non-1 patients had a significantly higher chance of achieving a sustained virological response. Of the characteristics during treatment only a negative result in transcription mediated amplification test (TMA) at week 6 had a high predictive value for sustained virological response, 80% in all patients and 92% in genotype non-1 patients. When treatment was continued for 22 weeks with ribavirin and amantadine alone, no end of treatment virological response was observed. Although 60% of the patients had undetectable levels of hepatitis C virus HCV-RNA by PCR test after the 2-week induction schedule, maintenance therapy of ribavirin and amantadine alone could not prevent virological relapse in these patients shortly after the interferon medication was stopped.

In chapter 8 the same high dose interferon induction therapy of 2 weeks is again evaluated. Retreatment of non-responding patients to previous interferon monotherapy for 24 weeks, with interferon in combination with ribavirin or ribavirin/amantadine including this high dose interferon schedule, resulted in a sustained virological response of 33% and 43% respectively. After 2 weeks induction therapy, patients with a viral load decline of 2.5 log IU/mL or more had 80% chance to achieve a sustained virological response. Whereas a decline of less than 2.5 log IU/mL was predictive for a non-response in 90 % of the patients.

How to act when a needle stick injury infected a health care worker with the hepatitis C virus? The solution is been given in chapter 9.