Chronic hepatitis C: new diagnostic tools and therapeutic strategies

Damen, M.

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Chapter 9

HEPATITIS C TREATMENT

M. Damen¹, D. Bresters²

¹ Central Laboratory of the Blood Transfusion Service of the Netherlands Red Cross (CLB), Viral Diagnostic Department, Amsterdam, The Netherlands

² Wilhelmina Children’s Hospital, Utrecht, The Netherlands

INTRODUCTION

For a proper evaluation of the results of any treatment, including the treatment for hepatitis C, one should know the natural history of the disease and thereby why, where and how treatment should intervene with the natural course of the disease. It is important to establish if the costs and side effects of treatment counterbalance the favourable effects. In other words, how should the aim of treatment be defined?

Treatment of chronic hepatitis C (non-A, non-B hepatitis (NANB)) did not await the characterization of the hepatitis C virus (HCV) genome in 1989 [1]. It was already clear from the natural history of NANB hepatitis that it was necessary to try to intervene in the progression of this disease: over 50% of the NANB hepatitis patients, diagnosed by abnormal alanine aminotransferase (ALT) levels, developed chronic liver disease [2, 3]. We know now that 70-80% of the patients infected with the hepatitis C virus develop chronic hepatitis C, defined by anti-HCV positivity and HCV viremia (measured with nucleic acid amplification techniques) for longer than 6 months [4, 5]. A considerable proportion of the patients with chronic hepatitis C can go unobserved, because ALT levels can be normal for long periods of time and often there may be no symptoms present. However, several studies suggest that chronic hepatitis C is characterized by progression from chronic persistent and active hepatitis to liver cirrhosis in about 25% of the cases and more rarely to hepatocellular carcinoma (HCC) [6-10]. The presence of HCV viremia and not ALT elevation has shown to be the major predictor for the presence of histologically proven hepatitis in anti-HCV-positive patients [11-13]. Thus, although chronic hepatitis C can go unobserved in some patients, the eventual development of cirrhosis and HCC in a proportion of patients is a serious problem that warrants early therapeutic intervention. The main aim of treatment should be to interfere with progression of chronic hepatitis to cirrhosis by elimination of the HCV in an early stage of the disease.

HISTORY OF HEPATITIS NANB/C TREATMENT

Before the establishment of the viral origin of most cases of posttransfusion and community-acquired NANB hepatitis several investigators tried to treat these patients with corticosteroids. Their results indicated that prednisone was not effective and even harmful in NANB hepatitis [3, 14, 15]. The poor efficacy of corticosteroids led to attempts to treat this disease with antiviral agents. A pilot study with acyclovir carried out in 5 patients with chronic NANB hepatitis showed that a 10-day course of intravenous acyclovir had no apparent short- or long-term beneficial effect on ALT levels or liver histology [16]. Since interferon-alpha (IFN-alpha) had shown promise as a therapy for chronic hepatitis B and was known to inhibit the replication of a wide range of RNA and DNA viruses, it was a natural choice to try IFN-alpha as a possible therapeutic agent for chronic NANB hepatitis. The first (non-controlled) pilot study of IFN-alpha in 10 patients with well-documented chronic NANB hepatitis was conducted in 1986 by Hoofnagle et al. [17]. In this study 8 out of 10 patients showed a marked decrease in ALT levels within 1-4 weeks of the start of IFN treatment. In 2 patients therapy was stopped after 4 months and both showed a relapse, i.e. ALT levels returned to pretreatment values. Prolonged treatment (1 year) was, however, associated with a sustained improvement in ALT levels. In 3 patients who underwent a liver biopsy after 1 year of IFN therapy, a marked improvement in the degree of portal inflamma-
tion and a disappearance of parenchymal hepatocytic necrosis was seen. Also, IFN therapy was fairly well tolerated in this group of patients. Similar results in 3 patients with hypogammaglobulinemia and chronic NANB hepatitis were reported by Thomson et al. [18]. The preliminary results from these studies were sufficiently encouraging to have led to the initiation of several prospective, randomized controlled trials of IFN therapy by other investigators.

INTERFERON

Pharmacology [19-25]

In 1957 Isaacs and Lindenmann [23] recognized that the phenomenon of 'viral interference' was mediated by an anti-viral agent produced by the infected cells themselves. The agent was called interferon. Interferons belong to a large group of regulatory proteins (cytokines) involved in the human immune defense against viral and bacterial infections, tumors and foreign cells. There are three known types of human interferons: IFN-alpha, IFN-beta and IFN-gamma. IFN-beta and IFN-gamma both are encoded by one gene; IFN-beta is produced by fibroblasts, epithelial cells and macrophages after induction by viral or other foreign antigens; IFN-gamma is induced in T-lymphocytes by foreign antigens and is rarely also produced by natural killer cells. IFN-alpha is a group of structurally related subtypes encoded by about 23 genes on chromosome 9. Production of IFN-alpha is induced in leukocytes (B-lymphocytes, null-lymphocytes and monocytes/macrophages) by foreign cells, virus-infected cells and viral envelopes, bacterial cells, bacterial products and tumor cells.

Target cells are activated by the interferons by their binding to specific receptors on the cell surface. Two kinds of IFN receptors are recognized in man: type I for IFN-alpha and IFN-beta and type II for IFN-gamma. After binding of IFN to the target cell receptor, the IFN-receptor complex is internalized and induces the synthesis of effector proteins that mediate the actions of IFN.

In viral infections the most important IFN-alpha-induced effector proteins are dsRNA-dependent protein kinase (RDPK) and 2',5'-oligo-adenylate synthetase (OAS). RDPK phosphorylates initiation factor eIF-2a which inhibits the initiation of mRNA translation into viral proteins. OAS synthesizes adenylate oligomers, including 2',5'-OA-dependent endoribonuclease, which causes an enzymatical degradation of viral RNA. Apart from the direct antiviral activities, IFN-alpha has immunomodulatory effects that are important for its antiviral action. These effects are: enhancement of MHC-I and MHC-II receptor expression, modulation of cytokine receptor expression (II-2, TNF-alpha), enhancement of NK cell activity and modulation of B lymphocyte antibody production. These effects can be stimulating as well as inhibitory. The beneficial effects of IFN in HCV infection appear to be dependent mainly on its direct antiviral activities.

At present several highly purified forms of human IFN-alpha are commercially available for clinical use. The most commonly used interferons are recombinant IFN-alpha 2a and 2b and natural human lymphoblastoid IFN-alpha (a mixture of multiple IFN-alpha subtypes).

Results of IFN treatment in chronic hepatitis NANB/C

NANB studies: The first randomized, controlled trials for IFN-alpha treatment in chronic NANB/C hepatitis were started when serological assays for hepatitis C were not yet available. At that time the following inclusion criteria were used: a history of chronic
NANB hepatitis (by exclusion of other viral or nonviral causes of hepatocellular injury), ALT values elevated above 1.5-2 times the upper level of normal during at least 6 months, and a histologically proven chronic hepatitis [26-30]. In these trials patients were treated with IFN in a dosage of 1-3 million units (MU) three times a week (t.i.w.) for 6-12 months. Normal ALT levels at the end of the follow-up (usually 6 months after cessation of therapy) were considered a sustained response to treatment. Sustained ALT response rates varied from 7-47% and longer duration and higher dose tended to induce a higher sustained response rate. Tine et al. [31] performed a meta-analysis on these first randomized controlled trials. From this analysis it can be concluded that an initial ALT response was induced in about 50% of the patients, however, the response was sustained in only 25% of the patients. Furthermore, in this analysis, the dose (1 or 3 MU t.i.w.) or duration of treatment (6 or 12 months) did not influence the response rate significantly.

HCV studies: Shortly after the characterization of the hepatitis C virus, anti-HCV screening assays and somewhat later also anti-HCV confirmation assays (immunoblots) were developed. Furthermore, cDNA-PCR assays became available for the detection of HCV-RNA in plasma. By means of these assays hepatitis C patients can be distinguished from non-A-E hepatitis patients and HCV viremic patients from HCV nonviremic patients. For the evaluation of papers in which the effect of treatment on viremia is studied, it should be kept in mind that PCR assays are only valid in the hands of specialized and experienced laboratories. In a recent quality control study for performance of HCV-RNA cDNA PCR, only 20% of the laboratories turned out to correctly diagnose viremic and nonviremic samples in a blinded panel [32].

In many recently published IFN trials, patients were retrospectively screened for pretreatment anti-HCV positivity and HCV viremia [33-36]. Pretreatment anti-HCV positivity varied from 88-98% and pretreatment HCV viremia varied from 75-96%. In four other recently published randomized, controlled trials anti-HCV positivity was part of the inclusion criteria, however the percentage of pretreatment viremia varied from 74-98% [37-40]. The studies mentioned above are among others analyzed in a recently published meta-analysis on 37 randomized, controlled trials for IFN treatment in chronic and acute hepatitis C published as full papers between 1989-1995 [41]. Inclusion criteria for all studies were comparable as mentioned above. This meta-analysis indicates that longer duration of IFN treatment (12 vs. 6 months) and higher dose of IFN treatment (5-6 vs. 3MU t.i.w.) both appeared to have a favorable effect on the sustained ALT response rate. However, the best overall results with the least side effects were obtained with a dosage of 3MU t.i.w. during 12 months in previously untreated (naive) patients with chronic hepatitis C.

Discrepancy in biochemical/virological/histological response: From the studies mentioned above it can also be concluded that an ALT response is not always accompanied by a virological response and that a virological response is not always accompanied by an ALT response. In the first situation IFN treatment does not eliminate the virus, but may have a temporarily beneficial influence on the hepatitis; in the second situation elevated ALT levels may reflect residual damaged hepatocytes, the presence of the virus in a titer below the PCR detection threshold or another cause of hepatitis. In the studies of Davis and Lau [42] and Chemello et al. [43] it is confirmed that biochemical response does not correlate well with virological response. Moreover, the biochemical response is not always accompanied by histological improvement and vice versa [26, 27, 35]. In a study of De Alava et al. [44] on the long-term histological outcome of IFN treatment in chronic HCV infection it is suggested that sustained HCV-RNA response is probably a better predictor of histological
<table>
<thead>
<tr>
<th>Author</th>
<th>Ref. No.</th>
<th>Treatment arms</th>
<th>Treatment period</th>
<th>Sample size</th>
<th>Sustained response: biochemical</th>
<th>virological</th>
<th>biochemical and virological</th>
<th>Follow-up period</th>
<th>Response predictors</th>
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<tr>
<td>Hopf et al.</td>
<td>45</td>
<td>IFN-alpha 2a 3MU t.i.w.</td>
<td>12 months</td>
<td>40</td>
<td>9 (23)</td>
<td>4 (22)</td>
<td>6 (26)</td>
<td>24-48 months</td>
<td>Genotype</td>
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<td></td>
<td></td>
<td>natIFN-alpha 3MU t.i.w.</td>
<td>6-12 months</td>
<td>18</td>
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<td>natIFN-alpha 5MU t.i.w.</td>
<td>6-12 months</td>
<td>23</td>
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<tr>
<td>Rumi et al.</td>
<td>46</td>
<td>IFN-alpha 2a 6MU t.i.w.</td>
<td>12 months</td>
<td>116</td>
<td>19 (16)</td>
<td>10 (17)</td>
<td>12 months</td>
<td>Genotype, viral load, cirrhosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>natIFN-alpha 6MU t.i.w.</td>
<td>12 months</td>
<td>22 (19)</td>
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<tr>
<td>Shiffman et al.</td>
<td>47</td>
<td>IFN-alpha 2b 5MU t.i.w. + randomization (in ALT responders); Stop tapering period</td>
<td>6 months</td>
<td>92</td>
<td>21/92 (23)^a</td>
<td>292 (2)</td>
<td>292 (2)</td>
<td>12-18 months</td>
<td>None</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>21/92 (23)^a</td>
<td>16/92 (11)</td>
<td>13/92 (14)</td>
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<td>Brouwer et al.</td>
<td>48</td>
<td>IFN-alpha 2b 3MU t.i.w.</td>
<td>6 months</td>
<td>149</td>
<td>24 (16)</td>
<td>22 (15)</td>
<td>21 (14)</td>
<td>6 months</td>
<td>Genotype, viral load, cirrhosis</td>
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<tr>
<td></td>
<td></td>
<td>IFN-alpha 2b 6MU t.i.w. + ALT/PCR based titration period</td>
<td>2 months + variable</td>
<td>197</td>
<td>36 (19)</td>
<td>32 (17)</td>
<td>28 (15)</td>
<td></td>
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<tr>
<td>Yuki et al.</td>
<td>49</td>
<td>natIFN-alpha 5MU t.i.w.</td>
<td>6 months</td>
<td>45</td>
<td>15 (33)</td>
<td></td>
<td></td>
<td>6 months</td>
<td>Genotype, viral load</td>
</tr>
<tr>
<td></td>
<td></td>
<td>natIFN-alpha 5MU t.i.w.</td>
<td>12 months</td>
<td>43</td>
<td>23 (54)</td>
<td></td>
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<tr>
<td>Friedlander et al.</td>
<td>50</td>
<td>IFN-alpha 5MU t.i.w.</td>
<td>6 months</td>
<td>31</td>
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<tr>
<td></td>
<td></td>
<td>IFN-alpha 5MU daily till virological response</td>
<td>8-11 months</td>
<td>14</td>
<td></td>
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<td></td>
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<tr>
<td>Hakozaki et al.</td>
<td>51</td>
<td>IFN-alpha 2b 3MU t.i.w.</td>
<td>6 months</td>
<td>26</td>
<td>6 (23)</td>
<td>6 (23)</td>
<td>12 months</td>
<td>n.a.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>IFN-alpha 2b 6MU t.i.w.</td>
<td>6 months</td>
<td>35</td>
<td>15 (43)</td>
<td>14 (40)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>IFN-alpha 2b 10MU t.i.w.</td>
<td>6 months</td>
<td>30</td>
<td>11 (37)</td>
<td>10 (33)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Toyoda et al.</td>
<td>52</td>
<td>natIFN-alpha 6 MU/day + 6 MU t.i.w.</td>
<td>2 weeks + 22 weeks</td>
<td>32</td>
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<tr>
<td></td>
<td></td>
<td>natIFN-alpha 6 MU/day + 6MU t.i.w.</td>
<td>8 weeks + 12 weeks</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rechard et al.</td>
<td>53</td>
<td>IFN-alpha 2b 3 MU t.i.w.</td>
<td>14 months</td>
<td>40#</td>
<td>14 (35)</td>
<td>17 (43)</td>
<td>14 (35)</td>
<td>6 months</td>
<td>n.a.</td>
</tr>
<tr>
<td>Wieland et al.</td>
<td>54</td>
<td>natIFN-alpha 3 MU t.i.w. (stop in ALT non-responders after 4 months)</td>
<td>6 months</td>
<td>40</td>
<td>8 (20)</td>
<td>9 (23)</td>
<td>6 (15)</td>
<td>6 months</td>
<td>Genotype, viral load, histology</td>
</tr>
<tr>
<td>Author</td>
<td>Ref. No.</td>
<td>Treatment arms</td>
<td>Treatment period</td>
<td>Sample size ( ^a )</td>
<td>Sustained response ( ^b )</td>
<td>Virological</td>
<td>biochemical and virological</td>
<td>Follow-up period</td>
<td>Response predictors</td>
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<tr>
<td>Yamada et al.</td>
<td>55</td>
<td>natIFN-alpha 9 MU i.w. (hemophilia pt.)</td>
<td>6 months</td>
<td>20</td>
<td>11 (55)</td>
<td>10 (50)</td>
<td>18 months</td>
<td>Genotype, viral load</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>natIFN-alpha 9 MU i.w. (other pt.)</td>
<td>6 months</td>
<td>24</td>
<td>n.a.</td>
<td>10 (42)</td>
<td></td>
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</tbody>
</table>

\( ^a \) Number of evaluable patients.

\( ^b \) Responder at the end of follow-up.

\( ^c \) Treatment is tempered to 3 MU i.w. in ALT responders.

\( ^d \) 46/92 patients were ALT responders after 6 months.

\( ^e \) Titration scheme also included cessation of IFN after 3 months in ALT nonresponders and after 12 months in partial ALT responders (ALT decrease > 50%).

\( ^f \) Nonrandomized trials.

\( ^g \) In retrospect 1 ALT nonresponder was HCV-RNA-negative during the whole study period.

\( ^h \) not available.
Improvement than the sustained ALT response. In a study of Prieto et al. [12] among 98 anti-HCV-positive blood donors it is clearly demonstrated that HCV-RNA positivity is correlated with more severe histological findings as compared to HCV-RNA negativity.

**PCR-monitored HCV studies:** In table 1 an overview is presented of eleven studies in chronic hepatitis C patients treated with IFN [45-55]. Eligibility criteria for these studies were comparable and included an ALT elevation of at least 1.5-2 times the upper limit of normal for at least 6 months prior to inclusion, confirmed anti-HCV positivity, pretreatment HCV viremia and no other known viral or nonviral causes of hepatitis. The studies of Reichard et al. [53], Weiland et al. [54] and Yamada et al. [55] were nonrandomized trials, the others were randomized, controlled trials. In the studies reviewed, response criteria were defined uniformly. A sustained biochemical response is defined as normalization of the ALT level at the end of follow-up (at least 6 months); sustained virological response is defined as undetectable HCV-RNA at the end of follow-up (at least 6 months). A biochemical relapse is defined as the recurrence of pretreatment ALT levels after cessation of treatment in an initial (biochemical) responder. A virological relapse is defined as the recurrence of detectable HCV-RNA after cessation of treatment in an initial (virological) responder. In the studies reviewed in table 1 the duration of treatment varied between 6 and 14 months, sometimes including a response-dependent tapering period in which the IFN dosage varied between 3 and 9 MU t.i.w. Recombinant IFN-alpha as well as natural leucocyte-derived IFN-alpha were used, which appeared to have no influence on response rates [45]. Standard IFN treatment (3-6 MU t.i.w. 6 months) resulted in a 2-23% sustained virological response, whereas an increase in dose or duration of treatment increased virological sustained response rates to 42-50%.

### Predictors of response:

In 8 of the 11 trials in table 1, pretreatment predictors for response were studied. In most trials sustained virological responders had a significantly lower pretreatment viral load compared to non-(sustained)-responders. Furthermore, patients with HCV genotypes other than 1 or 1b more frequently had a sustained response as compared to patients with genotype 1 or 1b. Probably, different HCV strains have a different susceptibility to the antiviral actions of IFN. On the other hand, the HCV genotype is a difficult item to study as a predictive factor for response because of the variable prevalence of HCV genotypes in different areas and populations. Correcting for this bias, some investigators only observed a correlation between response and low pretreatment viral load and not with HCV genotype [56-58]. This phenomenon is confirmed in a study on the pathogenicity of the different HCV genotypes by Benvegnu et al. [59]. They suggested that the genotype 1b existed in the population for a longer period of time than other genotypes and was thus more frequently found in patients with a longer duration of infection and worse liver histology (and probably worse response to treatment).

Another possible predictor of nonresponse, which was not studied in the reviewed trials, may be the degree of quasispecies diversity. In vivo, HCV exists as a mixture of heterogeneous quasispecies. In four recently published Japanese studies poor response to IFN correlated with a high degree of quasispecies variability [60-63]. Furthermore, IFN-resistant strains may be selected during IFN treatment [64]. Enomoto et al. [65, 66] found that IFN-sensitive genotype 1b strains significantly more often had a mutation in the NS5A region than IFN-resistant genotype 1b strains.

### IFN retreatment:

Up to 50% of the responding (biochemical or virological) patients relapse after cessation of IFN treatment. In these patients retreatment with a second course of IFN therapy may be worthwhile. Weiland et al. [67] performed a pilot study in 10 virological
relapsers after a 6-month course of IFN. During the second 6-month course of IFN (3 MU t.i.w.) 5 patients again had a virological response, however all relapsed after treatment cessation. Gerken et al. [68] found 40% sustained virological response after a 6-15 month retreatment course (5-6 MU t.i.w.) in 20 virological relapsers. Furthermore, Rabinovitz et al. [69] found a 43% sustained virological response in the retreatment of IFN relapers and a 13% sustained virological response in the retreatment of IFN nonresponders. In our hands, 8/10 virological relapsers after a 6-month IFN treatment course showed a sustained virological response after a 2-year retreatment course [Damen et al., unpubl. observations]. Thus, long-term retreatment seems to be effective, especially in patients who relapse.

IFN treatment in patients with normal ALT: Historically, only hepatitis C patients with elevated ALT levels have been treated with IFN. However, since HCV-RNA positive patients with normal ALT levels appear to have an abnormal liver histology, varying from chronic persistent hepatitis to active cirrhosis [11, 70], treatment of this patient group may be worthwhile. In the study of van Thiel et al. [70] 37 HCV-RNA-positive patients with normal ALT levels were treated with IFN 2b 5 MU daily for a period of 1 year or shorter when three consecutive HCV-RNA tests performed monthly were negative. 24/37 patients had a virological response and 21/37 (57%) had a sustained virological response. Unfortunately, no posttreatment liver biopsy is reported in this study. By contrast, in a pilot study of Serfati et al. [71] treatment of 10 HCV-RNA-positive patients with normal ALT levels (IFN 3 MU t.i.w. for 6 months) revealed no sustained virological response in any of the patients. Seven patients underwent liver biopsy before and after treatment and showed no significant changes. ALT elevations during or after IFN treatment were not reported in the study of van Thiel et al. and in the study of Serfati et al. temporarily slight or moderate ALT elevations were reported in 6 cases during IFN treatment. Probably, a more aggressive form of treatment is needed to clear the virus in this patient group.

Histological response: In four of the studies reviewed in table 1 [45-47, 53], the histological response was also studied. In all studies the mean histological activity index improved significantly during treatment and this improvement was more pronounced in virologically responding patients. A few studies focused primarily on liver histology during and after treatment. A study of Reichard et al.[72], in virological nonresponders, showed histological improvement in 4 of the 9 patients after 2-3 IFN treatment courses. In four other studies it was observed that IFN treatment caused a regression of liver fibrosis and suppression of active fibrogenesis [73-76]. This effect was irrespective of a biochemical or virological response. Two recent studies focused on the role of IFN in preventing HCC [77, 78]. In both trials, patients with HCV-related liver cirrhosis were treated with IFN-alpha and compared with an untreated control group during a follow-up period of 2-7 years. In the study of Nishiguchi et al. [78] 16% showed a sustained virological response following treatment. In the study of Mazzella et al. [77] virological response is not studied. In both studies the incidence of HCC was significantly lower in IFN-treated patients as compared to the controls. In the IFN-treated groups HCC developed only in the virologically nonresponding patients. Thus, apart from antiviral effects, IFN may have beneficial effects on the course of chronic HCV infection with respect to liver damage and the development of HCC.

IFN treatment in acute HCV infection
Several investigators performed IFN treatment studies in patients with acute HCV infection in an attempt to prevent the development of chronic hepatitis C. In table 2, five randomized, PCR-monitored studies are reviewed. Inclusion criteria for the studies varied as shown. This
<table>
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<th>Author</th>
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<th>Treatment period</th>
<th>Sample size</th>
<th>Sustained response&lt;sup&gt;b&lt;/sup&gt; biochemical</th>
<th>Sustained response&lt;sup&gt;b&lt;/sup&gt; virological</th>
<th>Biochemical and virological</th>
<th>Follow-up period</th>
<th>Inclusion criteria</th>
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<td>Alberti et al.</td>
<td>79</td>
<td>IFN-alpha 2a 6 MU t.i.w. Untreated controls</td>
<td>4-6 months</td>
<td>11</td>
<td>8 (73)</td>
<td>7 (64)</td>
<td>12 months</td>
<td>&gt;10-fold elevated ALT, anti-HCV-positive, exclusion other causes</td>
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<td></td>
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<td>4-6 months</td>
<td>10</td>
<td>2 (20)</td>
<td>2 (20)</td>
<td></td>
<td>12 months</td>
<td>&gt;2-fold elevated ALT, posttransfusion, HCV-RNA-positive</td>
</tr>
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<td>Hwang et al.</td>
<td>80</td>
<td>IFN-alpha 2b 3 MU t.i.w. Untreated controls</td>
<td>3 months</td>
<td>16</td>
<td>9 (56)</td>
<td>7 (44)</td>
<td>2 (13)</td>
<td>18 months</td>
<td>&gt;2.5-fold elevated ALT, posttransfusion, anti-HCV-positive, exclusion other causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 months</td>
<td>17</td>
<td>6 (38)</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td></td>
<td>ALT elevated &gt;200 U/L, posttransfusion or acute onset hepatitis, exclusion other causes</td>
</tr>
<tr>
<td>Lampertico et al.</td>
<td>81</td>
<td>IFN-alpha 2b 3 MU t.i.w. Untreated controls</td>
<td>3 months</td>
<td>18/22&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13/22 (59)</td>
<td>7/18 (59)</td>
<td>4/18 (22)</td>
<td>18 months</td>
<td>&gt;2.5-fold elevated ALT, posttransfusion, anti-HCV-positive, exclusion other causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 months</td>
<td>9/16&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6/16 (37)</td>
<td>0/9 (0)</td>
<td>0/9 (0)</td>
<td></td>
<td>ALT elevated &gt;200 U/L, posttransfusion or acute onset hepatitis, exclusion other causes</td>
</tr>
<tr>
<td>Orita et al.</td>
<td>82</td>
<td>IFN-beta 3 MU/day + 3 MU t.i.w. + 2nd course optional&lt;sup&gt;1&lt;/sup&gt; Untreated controls</td>
<td>5 days</td>
<td>10/11&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9/10 (90)</td>
<td>9/10 (90)</td>
<td>9/10 (90)</td>
<td>36 months&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt;2.5-fold elevated ALT, posttransfusion or acute onset hepatitis, exclusion other causes</td>
</tr>
<tr>
<td>Takano et al.</td>
<td>83</td>
<td>IFN-beta 0.3 MU/day</td>
<td>28 days</td>
<td>11/17&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2/11 (18)</td>
<td>1/9 (11)</td>
<td>1/9 (11)</td>
<td>6 months</td>
<td>&gt;2.5-fold elevated ALT, posttransfusion or acute onset hepatitis, exclusion other causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFN-beta 3 MU/day</td>
<td>56 days</td>
<td>10/16&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0/10 (0)</td>
<td>0/10 (0)</td>
<td>0/10 (0)</td>
<td></td>
<td>&gt;2.5-fold elevated ALT, posttransfusion or acute onset hepatitis, exclusion other causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFN-beta 3 MU/day</td>
<td>28 days</td>
<td>13/17&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6/13 (46)</td>
<td>5/12 (42)</td>
<td>5/12 (42)</td>
<td></td>
<td>&gt;2.5-fold elevated ALT, posttransfusion or acute onset hepatitis, exclusion other causes</td>
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<tr>
<td></td>
<td></td>
<td>IFN-beta 3 MU/day</td>
<td>56 days</td>
<td>12/17&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5/12 (42)</td>
<td>4/9 (44)</td>
<td>4/9 (44)</td>
<td></td>
<td>&gt;2.5-fold elevated ALT, posttransfusion or acute onset hepatitis, exclusion other causes</td>
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<td></td>
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<td>IFN-beta 6 MU/day</td>
<td>28 days</td>
<td>9/15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4/9 (44)</td>
<td>2/9 (22)</td>
<td>2/9 (22)</td>
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<td>&gt;2.5-fold elevated ALT, posttransfusion or acute onset hepatitis, exclusion other causes</td>
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<td>IFN-beta 6 MU/day</td>
<td>56 days</td>
<td>10/15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9/10 (90)</td>
<td>1/9 (11)</td>
<td>1/9 (11)</td>
<td></td>
<td>&gt;2.5-fold elevated ALT, posttransfusion or acute onset hepatitis, exclusion other causes</td>
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</tbody>
</table>

Figures in parentheses represent percentage.
<sup>a</sup> Number of evaluable patients.
<sup>b</sup> Responder at end of follow-up.
<sup>c</sup> Proportion of patients with detectable HCV-RNA in plasma before treatment.
<sup>1</sup> Identical second treatment course in ALT nonresponders.
<sup>2</sup> Total study period, posttreatment period varied from 24-35 months.
<sup>3</sup> 20/26 sustained PCR responders also sustained ALT responders.
was due to the fact that in the different studies treatment was started at different clinical stages after HCV transmission (ALT elevation and/or anti-HCV-positive and/or presence of HCV-RNA). In table 2 the virological response in patients who were HCV-RNA-positive before treatment (in retrospect) was reviewed. In four studies IFN-alpha or IFN-beta treatment was compared with no treatment [79-82]. Clearly, the IFN-treated groups had a higher proportion of sustained virological responders as compared to the untreated control groups. In the study of Takano et al. [83] different IFN-beta treatment protocols were compared and the highest dose regimen (6 MU/day during 56 days) apparently revealed the highest virological response rate. In a recent meta-analysis on IFN treatment of acute hepatitis C, among them the studies reviewed above, 52/100 treated patients had a sustained virological response compared to 8/70 untreated patients [84].

In two other studies, in which unfortunately no PCR data were available, liver-biopsies were taken after IFN treatment [85, 86]. In the study of Viladomiu et al. [85] only minor histological improvement was observed in the treatment group as compared to the control group. However, the only inclusion criterion in this study was acute post-transfusion NANB hepatitis. In the study of Ohnishi et al. [86] 4/12 IFN-treated patients with acute HCV infection showed normal liver histology 1-2 years posttreatment and 1/12 showed marked improvement.

**IFN treatment of chronic hepatitis C in children**

Only few studies have been performed on the treatment of hepatitis C in children. Komatsu et al. [87] performed an open study in 13 children between 5 and 17 years old. The IFN dose was 0.1 MU/kg daily for 2 weeks followed by the same dosage t.i.w. during 22 weeks. A sustained virological response was observed in 5/13 (38%) children. Iorio et al. [88] treated 11 children with 3 MU/m² during 12 months and compared the results with a control group of 10 untreated children. 5/11 treated children (45%) had a sustained virological response versus 1/10 (10%) controls. In all treated patients (responders as well as nonresponders), liver histology after treatment was significantly improved as compared to pretreatment histology. Bortolotti et al. [89] treated 14 children with 5 MU/m² t.i.w. during 12 months and compared the results with a control group of 13 untreated children. A sustained virological response was observed in 69% of the treated children and in none of the controls. In general, treatment was well tolerated by the children. Apart from the known side effects of IFN in adults, one case of febrile convulsions and one case of mild transient heart failure was observed among the children in the studies mentioned above. The latter side effect occurred in a child which had received intensive chemotherapy (including doxorubicin) for acute lymphoblastic leukemia. Although patient numbers are limited, sustained virological response rates appear to be higher in children than in adult patients.

**Side effects of IFN treatment**

The most common side effect seen in almost all IFN-treated patients is a 'flu-like' syndrome, including fever, chills, myalgia, headaches and general malaise, symptoms which typically improve or resolve after the first few doses of the drug and can be alleviated by paracetamol [26, 27]. Other symptoms that can accompany IFN treatment are fatigue, lethargy, irritability, depression, sexual dysfunction, dizziness, seizures, anorexia, nausea, vomiting, diarrhea, weight loss, retinal abnormalities, mild alopecia, pruritus, cutaneous necrosis on the injection sites, cytopenia (leukopenia, thrombocytopenia) and inducement of autoantibodies [29, 30, 90-92].
Of special consideration is the leukopenia and thrombocytopenia which often develop with IFN treatment due to bone marrow suppression [93, 94]. Thrombocytopenia during IFN treatment can also be caused by autoantibodies against thrombocytes [94, 95]. It is important to regularly monitor leukocyte and thrombocyte counts during IFN treatment and if necessary reduce the IFN dose or even stop treatment. Like all side effects caused by IFN, the cytopenia is reversible after dose reduction or cessation of treatment.

Of importance also are the psychiatric effects of IFN treatment, of which depression is the most common [96, 97]. Renault et al. [96] describe three psychiatric syndromes that can occur during IFN treatment: an organic personality syndrome characterized by irritability and short temper; an organic affective syndrome characterized by emotional lability, tearfulness, depression and feelings of hopelessness; and a delirium, developing only in patients with a previous history of brain injury or brain dysfunction. These psychiatric side effects were more likely to occur with a higher IFN dose. The psychiatric side effects are potentially serious and often need dose adjustment or cessation of IFN treatment. Warning patients and their families of these side effects at the start of therapy is important.

A major side effect of IFN treatment is the inducement of autoantibodies of several kinds, which can lead to clinically significant problems. Clinically apparent hyperthyroidism or hypothyroidism has been described by several investigators to be caused by autoantibodies (antithyroid microsomal antibodies and antithyroglobulin antibodies) induced by IFN treatment [27, 29, 98-100]. Other autoantibodies that can be induced by IFN treatment are antinuclear antibodies, smooth muscle antibodies, and antiparietal cell antibodies [101, 102]. In contrast to thyroid autoantibodies these autoantibodies usually do not give rise to a clinical autoimmune disease. Antibodies can also be directed at IFN itself, but the presence of these antibodies does not appear to or appears only rarely to influence the response to IFN treatment [103-105]. In a report of Hanley et al. [106] a correlation was found between the development of IFN antibodies and a breakthrough during treatment. Only in case of a breakthrough may the detection of IFN antibodies be of clinical significance.

A recently recognized side effect of IFN-alpha is the development of retinal abnormalities including hemorrhage, cotton wool spots and retinal nerve fiber layer defects during IFN treatment. These abnormalities are thought to be related to disturbances in the retinal microcirculation. In a study of Kawano et al. [107] retinal abnormalities developed in 57% of the 63 patients during IFN treatment. However, the majority of the patients had no complaints of the retinal abnormalities. Retinopathy tended to occur in correlation with a decrease of the white blood cell count and platelet count.

Liver failure with fatal outcome probably due to IFN treatment was described in a patient with HBeAg-positive hepatitis B and in a patient with chronic myelogenous leukemia [108, 109]. Especially in decompensated liver cirrhosis patients should be monitored carefully [110]. Furthermore, in undiagnosed autoimmune hepatitis, IFN treatment can lead to acute decompensation of liver disease [111]. Patients with a combination of chronic hepatitis C and autoimmune hepatitis with IFN treatment should be monitored carefully [112, 113].

**RIBAVIRIN**

*Pharmacology [114,115]*

Ribavirin (1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is an antiviral agent with inhibitory activity against a broad spectrum of viral pathogens, including both DNA and RNA viruses. This drug was shown to be successful as an aerosol for respiratory syncytial
virus pneumonia in children. It has not been extensively studied for effects in other viral infections but a few trials in patients infected with human immunodeficiency virus (HIV), hepatitis B virus, influenza virus and Lassa fever virus were performed [116-119]. Ribavirin is an analogue of the nucleoside guanosine, but unlike other antiviral agents it has a modified base instead of a modified sugar. Ribavirin exerts its antiviral effects after intracellular phosphorylation to mono-, di- and especially triphosphate nucleotides. The molecular mode of action of this agent is still controversial, but several theories have been proposed. One hypothesis is that treatment with this agent leads to decreased intracellular pools of guanosine triphosphate (GTP), thereby indirectly suppressing the synthesis of viral nucleic acid. This effect results from the inhibition of the enzyme inosine monophosphate dehydrogenase. Another hypothesis is that ribavirin induces the synthesis of RNA with abnormal or no 5' cap structures in virus-infected cells, leading to inefficient translation of viral transcripts. A third hypothesis states that ribavirin has a direct suppressive effect on viral RNA-dependent RNA polymerase. This effect may be mediated by several phosphorylated forms. The primary mechanism of action has not been established, but it is likely that ribavirin acts in a multiple-site fashion.

Results of ribavirin treatment in chronic hepatitis C
A few studies on ribavirin monotherapy in chronic hepatitis C have been performed [120-123]. The studies of Camps et al. [120] and Reichard et al. [121] were noncontrolled pilot studies in IFN non-responders and naive patients, respectively. In both studies ALT levels decreased or normalized during treatment but rose to pretreatment values after cessation of therapy. HCV-RNA remained detectable in plasma during ribavirin treatment. However, in the study of Reichard et al. the mean viral load decreased temporarily during treatment. The studies of DiBisceglie et al. [122] and Dusheiko et al. [123] were randomized placebo-controlled studies investigating a 12- and a 6-month course of ribavirin monotherapy with 1,000-1,200 mg/day in two daily doses, respectively. The number of patients studied was 58 in the study of DiBisceglie et al. (29 treated vs. 29 controls) and 114 in the study of Dusheiko et al. (76 treated vs. 38 controls). Inclusion criteria in both studies were elevated ALT levels, anti-HCV positivity and detectable HCV-RNA in plasma. In both studies ALT levels decreased or normalized in the ribavirin-treated patients significantly more often than in the placebo-treated patients, however the majority of patients relapsed after cessation of treatment. The HCV-RNA load did not change significantly in either of the studies during ribavirin treatment as compared to placebo treatment. In the study of DiBisceglie et al. a decrease in hepatic inflammatory activity and necrosis was observed in the ribavirin-treated patients who had a normalization of their ALT levels. However, in the study of Dusheiko et al. no significant improvement of the liver histology was observed in the ribavirin-treated group as compared to the control group. In conclusion, ribavirin monotherapy was not shown to be effective in the treatment of chronic hepatitis C.

Results of ribavirin/IFN combination treatment in chronic hepatitis C
To date a number of pilot studies have been undertaken to evaluate the efficacy of IFN-alpha therapy in combination with ribavirin in chronic hepatitis C. In table 3, six PCR-monitored studies are shown. In all studies inclusion criteria were elevated ALT levels, anti-HCV positivity and detectable HCV-RNA in plasma. In all studies IFN was administered in a dose of 3 MU t.i.w. and the treatment period was 6 months. The dose of ribavirin varied from 800-1,200mg/day in 2-3 daily doses. Four studies were randomized [124-127] and two
<table>
<thead>
<tr>
<th>Author</th>
<th>Ref. No.</th>
<th>Patient group</th>
<th>Treatment arms</th>
<th>Treatment period</th>
<th>Sample size&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sustained response&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lai et al.</td>
<td>124</td>
<td>naive&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Untreated controls, IFN-alpha 2α 3 MU t.i.w., IFN-alpha 2α 3 MU t.i.w. + ribavirin 400 mg twice a day</td>
<td>6 months</td>
<td>20&lt;sup&gt;d&lt;/sup&gt;</td>
<td>n.a.</td>
<td>24 months</td>
</tr>
<tr>
<td>Chenello et al.</td>
<td>125</td>
<td>naive</td>
<td>ribavirin 15 mg/kg per day, i.e. IFN-alpha 3 MU t.i.w.</td>
<td>6 months</td>
<td>14&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0</td>
<td>12 months</td>
</tr>
<tr>
<td>Brillanti et al.</td>
<td>126</td>
<td>nonresponders</td>
<td>IFN alpha 3 MU t.i.w. + ribavirin 400 mg twice a day, i.e. IFN alpha 3 MU t.i.w.</td>
<td>6 months</td>
<td>7</td>
<td>0</td>
<td>6 months</td>
</tr>
<tr>
<td>Brouwer et al.</td>
<td>127</td>
<td>nonresponders</td>
<td>placebo or ribavirin 1,000/1,200 mg per day</td>
<td>6 months</td>
<td>29</td>
<td>0</td>
<td>6 months</td>
</tr>
<tr>
<td>Schwartz et al.</td>
<td>128</td>
<td>nonresponders</td>
<td>IFN-alpha 2α 3 MU t.i.w. + ribavirin 1,000/1,200 mg per day</td>
<td>6 months</td>
<td>15</td>
<td>3</td>
<td>6 months</td>
</tr>
<tr>
<td>Bracco et al.</td>
<td>129</td>
<td>all&lt;sup&gt;f&lt;/sup&gt;</td>
<td>natIFN-alpha 3 MU t.i.w. + ribavirin 1,000/1,200 mg/d</td>
<td>6 months</td>
<td>15</td>
<td>9</td>
<td>6 months</td>
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</tbody>
</table>

<sup>a</sup> Figures in parentheses represent percentage.
<sup>b</sup> n.a. = not available.
<sup>c</sup> natIFN-alpha = natural human lymphoblastoid IFN-alpha.
<sup>d</sup> Number of evaluable patients.
<sup>e</sup> Response at the end of follow-up.
<sup>f</sup> No previous antiviral treatment.
<sup>g</sup> 1/60 patients retrospectively HCV-RNA-negative during the whole study.
<sup>h</sup> 3/45 patients were HCV-RNA-negative at pretreatment screening and are not evaluated here.
<sup>i</sup> Given in 2 daily doses; if >75 kg 1,200 mg/day and if ≤75 kg 1,000 mg/day.
<sup>j</sup> Nonrandomized trials.
<sup>k</sup> 13 naive patients, 1 IFN nonresponder and 1 IFN relapser, both sustained responder in combination treatment.
were nonrandomized [128, 129]. The patients included varied from IFN (virological) nonresponders and relapers to naive patients. In naive patients the sustained virological response to the combination therapy varied between 43 and 60%, in IFN relapers between 75 and 90% and in IFN nonresponders between 13 and 30%. In three studies liver histology was also evaluated [124, 126, 129]. All three studies showed a marked improvement of necroinflammatory features in sustained virological responders to the combination therapy. Although the patient numbers are limited, the results in these studies are promising.

Side effects of ribavirin treatment
In the four studies on ribavirin monotherapy side effects were mild and the drug was tolerated well [120-123]. The most important side effects were mild hemolytic anemia (in a few cases dose reduction was necessary), a concordant rise in the total bilirubin level and asymptomatic rises in serum uric acid levels (ribavirin is metabolized to urates). Other side effects were mild abdominal discomfort, skin disorders (pruritus, rash, alopecia, dry skin, eczema, herpes flare-up, hirsutism), upper respiratory tract inflammation, and nervous system disorders (depression, insomnia, nervousness, paraesthesia, somnolence, vertigo). In the reviewed studies on IFN/ribavirin combination treatment no side effects were reported other than those already known with IFN and ribavirin monotherapy [124-129].

OTHER THERAPEUTIC STRATEGIES
Several small trials have been undertaken to study the efficacy of IFN-beta [130], ursodeoxycholic acid [131-133], acyclovir [16,134], GM-CSF [135] and corticosteroids [112,136] in chronic hepatitis C. However, none of these agents showed significant results regarding viral clearance. An important issue in the search for new antiviral drugs in hepatitis C is the lack of an efficient cell culture or animal model for HCV infection which would allow screening of possible agents. Recently, the molecular structure of the HCV protease was described, which may lead to the in vitro development of protease inhibitors [134,137].

LIVER TRANSPLANTATION FOR CHRONIC HEPATITIS C
Complications of chronic hepatitis C infection are becoming a common reason for liver transplantation. Recurrence of the virus after transplantation has been reported in 86-100% of the patients with chronic hepatitis C [138,139]. However, the course of posttransplantation chronic hepatitis C has been reported to be mild and comparable to nontransplanted hepatitis C patients [140]. In three studies medium-term survival after hepatitis C related liver transplantation was studied [138, 139, 141]. Feray et al. [138] reported in a group of 79 transplanted HCV patients 68 cases of recurrent viremia. Of these patients 2 had a resolved infection, 28 developed chronic persistent hepatitis, 21 developed chronic active hepatitis and 1 developed cirrhosis within a mean follow-up period of 46 months (12-84 months). Ascher et al. [141] studied 97 patients after liver transplantation for hepatitis C-related cirrhosis and 59 patients after liver transplantation for cryptogenic cirrhosis, during a 3-year follow-up period. In this period 11/97 (11%) and 9/59 (15%), respectively, died. In the HCV group two of the deaths were directly related to recurrent HCV infection. Of the 95 surviving patients 41 developed recurrent hepatitis of whom 12 progressed to chronic active hepatitis. Gretch et al. [139] studied a group of 18 HCV-related liver transplantation patients during 2-4 years posttransplantation. All 18 patients
had recurrent HCV viremia and 9 developed chronic active hepatitis within 1 year posttransplantation. In the studies of Feray et al. and Gretchen et al., as well as in a study of Chazouilleres et al. [142] the posttransplantation viral titers were significantly higher (up to 16-fold) than the pretransplantation viral titers. This suggests that in some immune-compromised patients viremia with high viral titers is tolerated without or with little damage to the liver tissue.

In two studies the long-term outcome of HCV infection after liver transplantation was studied [140,143]. In the study of Gane et al. [143] 149 patients with HCV-related transplantation and 623 with non-HCV-related transplantation had a 5-year follow-up period. The 5-year survival rate of the HCV group was 70% and of the non-HCV group 69%. However, only 12% of the HCV patients had no evidence of chronic hepatitis in the most recent liver biopsy whereas 8% already had cirrhosis. Comparable results were observed by Böker et al. [140] in a study of 71 HCV patients up to 12 years posttransplantation. The 5- and 10-year survival rates were 62 and 62%, respectively. They observed no HCV-related deaths posttransplantation. The HCV-RNA carrier state without hepatitis in the liver biopsy was observed in 16% of the patients whereas 10% had cirrhosis in the liver biopsy at the time of the most recent checkup. In a report of Schlüter et al. [144] 10 of a group of 135 HCV-related liver transplantation patients were identified with severe recurrent hepatitis C infection. This severe infection required retransplantation in 9 patients and caused the death of 1 patient. No risk factors for this complication were identified. In conclusion, HCV viremia usually recurs after liver transplantation, but the course of the recurrent HCV infection is in most cases mild and comparable to that in nontransplanted patients and no extra disease was observed at the medium to long term as compared to liver transplantation patients without HCV.

In two studies of Feray et al. [145] and Wright et al. [146] recurrent HCV infection was treated with IFN. The sustained virological response rate was poor, 1/14 and 0/18, respectively. Histological improvement occurred in 2/14 and 0/18 patients. In the first study 5/14 treated patients developed chronic rejection in contrast to 1 case of chronic rejection in a control group of 32 patients. In the second study 1 case of possible chronic rejection was reported. Thus, treatment of recurrent HCV infection should be monitored very carefully if done in the first place. An interesting subject for future studies may be pretransplantation treatment in order to prevent recurrent HCV infection.

**ISSUES FOR FUTURE TREATMENT OF CHRONIC HEPATITIS C**

It is important to establish which goals should be achieved by treating patients with chronic hepatitis C, and whether the results of the treatment counterbalance the side effects. The most important aim of treatment is to achieve the sustained disappearance of HCV-RNA from plasma, because several studies have shown a correlation between the presence of HCV-RNA in plasma and abnormal liver histology. Elimination of the virus is supposed to prevent the development of liver cirrhosis and HCC.

The studies on IFN treatment that have been carried out so far show a sustained virological response rate in about 15-20% of the patients after 6 months of treatment. This result can be improved to maximally 40-60% by treatment schedules with longer duration of IFN treatment, higher dosage and especially retreatment in selected groups. The long-term prognosis after sustained virological response (6-12 months after cessation of treatment) is yet unknown. Therefore, sustained virological responders should be followed for life with
regular hepatological and virological checkups. Recent studies did show beneficial effects of IFN treatment on prevention of fibrosis and HCC, however this should be confirmed in larger prospective studies. An interesting question is whether continuous administration of low-dose IFN may prevent development of cirrhosis or HCC, even in virological nonresponders.

Recent pilot studies on IFN/ribavirin combination therapy have shown 13-30% sustained virological response in IFN nonresponders and 50-60% sustained virological response in naive patients after a 6-month therapeutic course. These promising results should be confirmed in larger randomized trials and also other treatment schedules of combination therapy (higher dose, longer duration) should be studied.

If more therapeutic options become available it would be worthwhile to focus on the susceptibility to treatment of the individual patient. Depending on viral and patient characteristics the physician should then choose the optimal treatment regimen.

In conclusion, future studies should focus on (1) prevention of cirrhosis and HCC with various therapeutic strategies, (2) treatment schedules combining IFN with ribavirin, (3) development of new antiviral therapeutics and combining them with IFN and/or ribavirin, (4) optimal therapeutic strategies for the individual patient.

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