Hepatitis C infection: the quest for new treatment strategies
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Citation for published version (APA):

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General introduction
**Discovery of the hepatitis C virus**

Hippocrates, in the fifth century BC, was the first person to describe a form of epidemic jaundice that was probably caused by viral hepatitis. Epidemics of jaundice caused by hepatitis have been described since then throughout history, and have been particularly common in times of war. The recognition of a form of hepatitis transmitted by blood products was first documented by Lurman in Germany in 1883 during a smallpox immunization campaign. Thousands of people received vaccine made from human lymph. Fifteen percent of them developed jaundice, while no such disease occurred among those who had not been vaccinated. In 1908 McDonald suggested that infectious jaundice was caused by a virus. In the year 1947 MacCallum classified viral hepatitis into two types: hepatitis A for “infectious” hepatitis transmitted by the fecal-oral route, and hepatitis B for “serum hepatitis” transmitted by the transfusion of blood products (1). These observations were confirmed in a series of studies by Krugman et al. in the 1960s and 1970s. These described two types of viral hepatitis, MS-1 and MS-2, in which MS-1 resembled hepatitis A and MS-2 hepatitis B (2). Around the same time Blumberg and Alter published their discovery of the Australian antigen that was later associated with the hepatitis B virus (HBV) (3). A couple of years later (1973) the hepatitis A virus was identified (4). The development of specific tests for the identification of the hepatitis B virus led to the introduction of hepatitis B surface antigen screening for all blood and blood products in the 1970s. However, post-transfusion hepatitis cases still occurred. It became apparent that these were being caused by one or more other viruses (non-A, non-B) (5). The virus in question was finally identified in 1989 and reported by Choo et al.; it was subsequently called hepatitis C virus (HCV) (6).

**HCV structure**

HCV is a member of the Flaviviridae family of viruses, which includes the pestiviruses, flaviviruses and hepacivirus (7). It is a small, enveloped RNA virus with a positive-sense single stranded genome of approximately 9,600 nucleotides. It encodes a single polypeptide that is post-translationally cleaved into 10 polypeptides including 3 structural (C, E1 and E2) and multiple non-structural proteins (NS), NS2 to NS5. The NS proteins include enzymes necessary for protein processing (proteases) and viral replication (RNA polymerase) (8-10). HCV replicates in the cytoplasm of hepatocytes where it is not directly cytopathic. Persistent infection appears to rely on the rapid production of virus and continuous cell-to-cell spread, along with a lack of vigorous T-cell immune response to HCV antigens. The rate of viral production in hepatitis C is high, in the range of $10^{10}$ to $10^{12}$ virions per day. There is also a rapid turnover of virus, at least in serum, the predicted half-life being 2 to 3 hours (11).

**HCV heterogeneity**

During viral replication errors may occur and consequently mutations may develop. As a result, HCV circulates in serum not as a single species but as a population of quasispecies (12;13). The quasispecies diversity of HCV may contribute to the development of chronicity during infection and may contribute to immune escape during anti-viral therapy. Six major genotypes (1 to 6) and more than 50 subtypes (e.g., 1a, 1b, 2a, 2b) of HCV have been described (12)
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Worldwide the different HCV genotypes are not equally distributed (14). Genotype 1a is common in the United States and Northern Europe. Genotype 1b has a worldwide distribution and is often found to be the most common genotype. Genotypes 2a and 2b are also worldwide in distribution and are particularly common in Japan and Northern Italy. Genotype 3 is most frequent in the Indian subcontinent; this genotype may have been introduced into the United States and Europe relatively recently, and may possibly have been spread by the injection of illegal drugs in the 1960s and 1970s, the hippie era. Genotype 4 is the most common genotype in Africa and the Middle East. Genotype 5 and 6 are rare and found in isolated geographical areas, genotype 5 in South Africa and genotype 6 in Hong Kong and Southeast Asia (15).

HCV detection

The diagnosis of an HCV infection is based on two categories of laboratory tests, namely serological assays detecting specific antibody to HCV (anti-HCV) and assays that detect, quantify, or characterize HCV-RNA in plasma. At present anti-HCV is identified by third-generation enzyme-linked immunosorbent assays (ELISA). Nucleic acid amplification techniques such as the polymerase chain reaction (PCR) and the transcription mediated amplification (TMA) are sensitive methods for the detection of HCV-RNA. These qualitative HCV-RNA tests discriminate between presence and absence of HCV in plasma; the detection limit of these tests varies from 5 to 50 IU/mL (16). Measurement of the amount of HCV-RNA in plasma can be performed by PCR or TMA techniques or by branched DNA (bDNA) assay. The detection limit of these quantitative tests varies from 30 to 615 IU/mL (17). In 1999 the World Health Organization established an international standard for HCV-RNA quantification and determined the international unit (IU), which is applied to all commercial HCV-RNA quantitative assays (18). HCV can be genotyped by direct sequence analysis, using reverse hybridization to genotype-specific oligonucleotide probes, or by restriction fragment length polymorphism analysis (19-21). Both methods identify the 6 HCV genotypes and a large number of subtypes.

HCV transmission

HCV is transmitted by percutaneous or permucosal exposure to infectious blood or blood-derived body fluids. Before the introduction of anti-HCV screening in Western countries in 1990, transfusion of blood and blood products was an important route of transmission (22). In hemophiliacs, the high prevalence of HCV infection of 46-76% rapidly fell to zero after the introduction of virucidal procedures for the preparation of plasma factor VIII concentrates (23). Other known risk factors associated with acquiring HCV infection (in the past), include transplantation of solid organs from infected donors, renal dialysis, injecting drugs, snorting cocaine, occupational exposure to blood and body fluids and mother-to-infant transmission (24-26). Currently, (in the USA) most newly acquired cases of HCV infection are associated with the injection of illegal drugs (68%), while 4% occur in health care workers frequently exposed to blood. This includes needle-stick injuries. Nosocomial, iatrogenic and perinatal exposures account for about 1% of all cases. In 9% of cases the source has not yet been identified, see figure 1.
General introduction

Figure 1  Sources of newly acquired HCV infections in the USA. Adapted from Alter (27).

![Pie chart showing sources of newly acquired HCV infections in the USA.](Image)

- Injection Drug Use: 68%
- Unknown: 9%
- Other: 1%*
- Occupational: 4%
- Sexual: 18%

* "Other" includes nosocomial, iatrogenic and perinatal infections

Whereas there is no controversy whether HCV is sexually transmissible, the contribution to the total number of HCV infected individuals is uncertain (28). A high degree of sequence homology between the viral strains of sexual partners has provided virological confirmation of that route of infection (29;30). However, the sexual transmission of HCV is much less efficient than that of other sexually transmitted viruses, including hepatitis B virus and human immunodeficiency virus (HIV). Eighteen percent of newly infected individuals in the USA had no other risk factors except exposure to an infected sex partner or to multiple sex partners, as shown in figure 1. However, other potential risk factors such as unacknowledged illegal intravenous or nasal drugs use, or sharing of razors, nail-grooming equipment, or toothbrushes, may also contribute to this high rate of HCV infection (31). Furthermore, the risk of HCV transmission by sexual contact differs by the type of sexual relationship. Persons in long-term monogamous partnerships are at lower risk (0-0.6% per year) (32) than those with multiple partners or those at risk for sexually transmitted diseases, including persons engaging in sexual practices that might traumatize the genital mucosa (0.4-1.8% per year). HIV co-infection certainly appears to increase the rate of HCV transmission by sexual contact (33-35). Barrier precautions for HCV positive individuals in long-term monogamous relationships are generally not recommended, in contrast to the recommendations for HCV positive individuals with multiple partners.
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Mother-to-infant transmission of HCV is uncommon. The rate of vertical transmission is 4-7% per pregnancy in women with HCV viremia, but co-infection with HIV causes a 4- to 5-fold increase in the rate of transmission. Elective caesarean section is not recommended for women with chronic HCV infection alone. Breastfeeding also poses no significant risk of HCV transmission, assuming that nipples are not traumatized (36). Although iatrogenic transmission of HCV is at present very rare in high income countries, it is still a very important transmission route in many areas of the developing world, due to unsafe injections, defined as reuse of a syringe or needles from patient to patient without adequate sterilization. Considering that 8-12 billion injections are given annually, and that 50% of these are unsafe in most of the developing world, this situation results in approximately 2.3-4.7 million HCV infections annually using a simple mass-action model (37).

HCV prevalence

Hepatitis C has now emerged as a silent epidemic, and is a major public health problem affecting 170 million people worldwide. The prevalence of HCV infection varies greatly from one country to the next. A national survey of a representative sample of non-institutionalized civilian Americans conducted between 1988 and 1994 indicates that 3.9 million Americans (1.8%) have been infected with HCV, of whom 2.7 million (74%) have ongoing chronic infection (38). The highest prevalence of HCV infection is found in Egypt, where 15-20% of the general population is infected due to parenteral antischistosomal mass treatment campaigns. In this country, which has the world’s greatest schistosomiasis problem, mass parenteral treatment had been administered with insufficiently sterilized injection equipment since the 1920s. When effective oral medication against Schistosoma infection became available in the 1970s, this transmission route of HCV infection came to an end (39). Southeast Asia has a prevalence rate of 5-10%, whereas in Western Europe prevalence rates of chronic HCV infection as low as <1% have been found (40).

HCV infection

After exposure to HCV, acute HCV infection is marked by the appearance of HCV-RNA in plasma within 1-2 weeks of exposure followed by alanine aminotransferase (ALAT) elevations 2-8 weeks after exposure, indicative of hepatocyte injury and necrosis. About one-third of adults with acute HCV infection also develop clinical symptoms and jaundice from 3 to 12 weeks after exposure, with an average of 7 weeks (41). Acute hepatitis C can be severe but is very rarely fulminant (42). Anti-HCV may arise at the time of onset of symptoms or thereafter, making anti-HCV testing unreliable for the diagnosis of acute HCV infection. Almost all patients eventually develop anti-HCV, although titers may be low or even undetectable in patients with immune deficiencies (figure 2).
Figure 2  Course of acute resolving hepatitis C infection
Adapted from Hoofnagle (15)

ALT=alanine aminotransferase level
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Figure 3  Course of acute hepatitis C infection that evolves into chronic infection
Adapted from Hoofnagle (15)

After an acute infection, clearance of HCV is observed in only 15-40% of cases. Most infected individuals develop chronic HCV infection as shown in figure 3, marked by persistence of HCV-RNA for at least six months after onset of infection. The rate of chronicity varies by age, sex, race, the presence of symptoms, or jaundice, and immune status (43-51). It is not known why the infection persists in some patients and resolves spontaneously in others.
Natural history of chronic HCV infection

The primary concern for patients with chronic hepatitis C, as it is for many other forms of chronic liver disease, is the development and evolution of fibrosis over many years, culminating in cirrhosis. Cirrhosis may lead to severe complications including portal hypertension, bleeding varices, encephalopathy, with a long term poor prognosis unless the patient is transplanted. The disease has also been recognized as a major risk factor for hepatocellular carcinoma (HCC), explaining the rise of HCC in the western world. In several retrospective studies, with an exposure interval of 20-30 years, cirrhosis was found to have occurred in 17-55% (mean 42%) of chronically infected individuals, HCC in 1-23% and liver-related death in 4-15% (52-56).

Prospective studies showed different outcomes, finding cirrhosis development in 7-16% (mean 11%), HCC in 0.7-1.3%, and liver related death in 1.3-3.7%. However, the duration of follow-up in these studies was relatively short, between 8 and 16 years (57-59). The results of a series of retrospective-prospective cohort studies involving young people were also different; a mean development of cirrhosis of 2.1% and no HCC was observed during an exposure interval of 10-50 years (45;48;50;51;60).

An examination of 57 studies of the natural history of HCV infection showed that after 20 years of HCV infection, cirrhosis had developed as follows:
* in 24% of the patients in longitudinal post-transfusion studies, with a mean age of 42 years at acquisition of infection;
* in 22% of the patients in cross-sectional studies involving patients referred to tertiary liver centers, with a mean age of 29 years at acquisition of infection;
* in 7% of patients in longitudinal community based studies, with a mean age of 26 years at acquisition of infection;
* in 4% of patients in cross-sectional surveys of newly diagnosed individuals at blood donor screening, with a mean age of 22 years at acquisition of infection (61).

In short, the natural history of chronic HCV is highly variable, influenced by host related and external factors. Age appears to be an important determinant of progression of chronic HCV infection. The younger the infection is acquired, the lower the rate of progression (62;63). But one issue remains unexplained. Does the rate of fibrosis progression increase as the affected person ages? One explanation for an exponential increase in the rate of fibrosis with advancing age is the inability of the aging immune system to cope with a pathological process (63). But it is still unproven whether the evolution of fibrosis plateaus over time, whether it increases at a linear rate, or whether there is an exponential increase in the rate of fibrosis.

Where the influence of sex is concerned, there is evidence that the rate of fibrosis progression is lower among women than among men (63;64). An important factor that accelerates fibrosis progression in chronic HCV infection is co-infection with HBV or HIV (65-67). Comorbidity such as hemochromatosis, non-alcoholic steatohepatitis (NASH), and schistosomiasis infection also play a role in a more rapid progression of fibrosis in persons with chronic HCV infection (68-71).
There is now ample evidence that persons with chronic HCV infection and normal values of the liver enzymes in plasma are likely to have fewer histological abnormalities in their liver biopsy than those with abnormal values of the liver enzymes. However, the combination of persistently normal liver enzymes with cirrhosis does sometimes occur (72;73). A major external factor with a proven relationship to disease progression to cirrhosis is alcohol intake of more than 50 grams/day, which also dramatically increases the risk of HCC (74). Despite all the knowledge that has been acquired, as mentioned above, it is still not possible to predict accurately in a given individual whether chronic HCV infection will remain stable or whether it will advance to cirrhosis or HCC.

Long-term complications of chronic HCV infection

The major potential long-term complications of chronic HCV infection are cirrhosis, symptomatic end-stage liver disease, and HCC. For persons not known to have chronic HCV infection, the progression to cirrhosis is often clinically silent until they develop the complications of end-stage liver disease. If symptoms do occur, the most common complaints are fatigue, abdominal pain, poor appetite, weight loss, and pruritus. The level of fatigue appears to correlate strongly with psychological factors, such as the presence of depression, rather than with histologic disease activity (75). Other possible complications of chronic HCV infection that affect quality of life more overtly are extrahepatic manifestestations. Hematological disorders may arise, such as essential mixed cryoglobulinemia and B-cell non-Hodgkin lymphoma. Cryoglobulinemia may lead to the deposition of circulating immune complexes in small to medium-sized blood vessels, and may involve the skin, the kidneys, peripheral nerves, and brain (76-79). A number of autoimmune phenomena and disorders have been associated with chronic HCV infection, including autoantibody formation (80;81), thyroid disease (82-85), sialoadenitis suggestive of Sjögren’s syndrome (86), diabetes mellitus (87-92), and myasthenia gravis (93;94). Chronic HCV infection has also been associated with ophthalmologic disorders including corneal ulcers, uveitis, scleritis, and sicca syndrome (95;96). Associated dermatological diseases are lichen planus (97) and porphyria cutanea tarda (98).

Treatment of chronic HCV infection: the past and the present

It is clear from the natural history of chronic HCV infection, that it is essential to try to intervene in the progression of the disease. The main aim of treatment is to eliminate the HCV at an early stage. Since interferon alpha (IFN) had shown promise as a treatment for chronic HBV infection and was known to inhibit the replication of a wide range of RNA and DNA viruses, it was a logical choice to explore IFN as a possible therapeutic agent. Interferons belong to a large group of regulatory proteins (cytokines) involved in the human immune defense against viral and bacterial infections and tumors (99). The most commonly used interferons in Western Europe are recombinant IFN 2a and 2b. The first pilot study of IFN in 10 patients with well documented chronic non A, non B hepatitis was conducted in 1986 and showed a marked decrease in ALAT levels after one year of treatment and a histological improvement in portal inflammation (100). The results of that study were sufficiently encouraging to initiate several randomized trials.
In 1991 the US Food and Drug Administration approved IFN in a dose of 3 million units (MU) subcutaneously thrice weekly (tiw) as a treatment for patients with chronic HCV infection. Since the availability of reliable HCV-RNA tests, the primary aim of therapy is to achieve a sustained viral response (SVR), which is defined as undetectable HCV-RNA six months after termination of antiviral therapy. Secondary goals of antiviral therapy include improvement in histological abnormalities, thus preventing cirrhosis and HCC.

A meta-analysis of IFN monotherapy trials, in which IFN 3 MU 3 tiw was given for six or twelve months, showed SVR rates of 8-12% respectively (101). Several factors were associated with a favorable response to IFN monotherapy: low pre-treatment HCV-RNA levels, HCV genotype 2 or 3, and absence of cirrhosis in a liver biopsy (101;102).

However, IFN treatment is associated with numerous side-effects. The most common of these is a flu-like illness that occurs in the first four weeks of therapy and that generally resolves on its own and can be alleviated by paracetamol. After the first month of treatment, late side-effects such as fatigue, headache and neuropsychiatric changes may occur, of which depression is the most common, although irritability, short temper and emotional liability are also frequently seen. Other symptoms that can accompany IFN treatment are sexual dysfunction, dizziness, seizures, anorexia, nausea, vomiting, diarrhea, weight loss, retinal abnormalities, mild alopecia, pruritus, cytopenia (leukopenia and thrombocytopenia) and induction of auto antibodies. Clinically apparent hyperthyroidism or hypothyroidism, due to IFN induced anti-thyroid microsomal antibodies and anti-thyroglobulin antibodies, is the auto-immune disorder seen most frequently (99).

Since low SVR rates were being achieved only at the cost of numerous side effects, it was obvious that better treatment schedules were needed.

Ribavirin is an antiviral agent with inhibitory activity against a broad spectrum of viruses, including both DNA and RNA viruses. Ribavirin monotherapy for chronic HCV patients decreased or normalized ALAT levels during therapy, but HCV-RNA levels did not change during treatment. Common side-effects associated with ribavirin include a dose-dependent hemolysis of red blood cells, skin disorders, upper respiratory tract inflammation, and nervous system disorders. Furthermore, ribavirin is potentially teratogenic (103).

However, the combination therapy IFN/ribavirin for chronic HCV patients showed promising results. In the first two large randomized controlled trials, in which the combination IFN/ribavirin was compared with IFN monotherapy, both given for 24 or 48 weeks, SVR rates of 33% and 41% respectively were found for the combination schedules, and 6% and 16% for the IFN monotherapy schedules. Genotype-1 patients treated with IFN/ribavirin combination for 24 or 48 weeks had SVR rates of 17% and 29% respectively. Genotype 2 and 3 patients achieved SVR rates of 66% and 65% respectively. This result yielded important treatment recommendations for genotype 2 and 3 patients: therapy duration could be reduced to 24 weeks. However, genotype-1 patients continued to need 48 weeks of therapy, and the outcome remained unsuccessful in almost 70% of those patients (104;105).

A favorable, additional effect of ribavirin is the reduction of the virological relapse. This defined as the recurrence of detectable HCV-RNA after cessation of treatment in a patient with an end-of-treatment response (ETR) (106).
Pre-treatment characteristics like viral load, genotype, histological features, sex, and young age were recognized as important predictors of therapy response (107). Subsequently, the viral response in the early phases of therapy (viral kinetics) became a most helpful tool during therapy. This could be done with evolving techniques for quantitative HCV-RNA testing, by which standardization of HCV-RNA load measurement became possible (108). The decline in HCV-RNA load seen during IFN therapy is biphasic (11;109;110).

Due to the pharmacokinetics of IFN, viral decline starts 7 to 10 hours after the first injection. The first phase or the initial decline is rapid and dose dependent. During the second phase, starting 48 hours after the start of therapy, viral levels decline much more slowly and the rate is variable. This second phase viral decline is predictive for SVR, as was observed in several studies (Table 1).

Table 1 Published positive predictors for SVR during IFN treatment.

<table>
<thead>
<tr>
<th>Positive predictors for SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>*3 log decline in HCV RNA viral load during the first 4 weeks (111)</td>
</tr>
<tr>
<td>*High rate of HCV RNA viral load decline during the second phase (11)</td>
</tr>
<tr>
<td>*HCV RNA viral load decline in the first 24 hours after administration of IFN beta (112)</td>
</tr>
<tr>
<td>*HCV RNA negative at week 4 by qualitative PCR test (113)</td>
</tr>
<tr>
<td>*HCV RNA negative at week 12 by qualitative PCR test (114)</td>
</tr>
<tr>
<td>*HCV RNA negative at week 2 by qualitative PCR test (115)</td>
</tr>
</tbody>
</table>

Testing HCV-RNA levels at the beginning of a course of treatment will not only identify those patients with a probable favorable outcome of therapy, but also those patients with a probable unfavorable outcome. When HCV-RNA was still detectable in patients at week 12 of an IFN monotherapy course of 24 or 48 weeks, 93% and 100% of them respectively did not achieve an SVR. Early stopping rules were postulated for these potentially non-responding patients to avoid further side-effects, as well as the costs and inconveniences of treatment (114;116-118).

In search of treatment with improved efficacy, high dose IFN induction schedules were introduced to achieve a more rapid viral decline and a higher rate of SVR (119). These schedules included the daily administration of IFN in one or more dosages. No significant differences in SVR rates between IFN induction schedules and standard IFN treatment schedules were found for naïve chronic HCV patients (120-124). However, for the difficult-to-treat patients, like genotype-1- non-responding patients during a previous treatment course, this approach enhanced the chance of a successful outcome (125;126).

More recently, the use of pegylated IFN has further improved SVR rates. With the addition of a polyethylene glycol (PEG) molecule to standard IFN, the renal clearance of IFN is delayed, prolonging the IFN half-life from approximately eight hours to several days. Treatment with PEG-IFN may improve phase 2 viral decline by means of permanent antiviral pressure on HCV replication (127).
Two PEG-IFN formulations are currently in use. PEG-IFN 2b: attachment of a 12 kilo Dalton linear PEG to the IFN alpha 2b molecule; and PEG IFN 2a: attachment of a 40 kilo Dalton branched PEG to the IFN alpha 2a molecule. Early phase trials of the two PEG-IFNs showed the practicality of the once-a-week injection instead of the three times weekly injection for the standard IFN, their efficacy in lowering HCV-RNA levels, and the absence of severe adverse events associated with the long plasma half-life (128;129). Three large randomized controlled trials compared standard IFN monotherapy with PEG-IFN (130-132). The SVR rates were twice as high with PEG-IFN compared with standard IFN (Table 2).

**Table 2**

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref.</th>
<th>Year</th>
<th>Therapy</th>
<th>No. of patients</th>
<th>ETR %</th>
<th>SVR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindsay et al.</td>
<td>131</td>
<td>2001</td>
<td>IFN alfa -2b 3MU tiw 48 weeks</td>
<td>303</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PEG-IFN 12 kDA (1.5 µg/kg/wk) 48 weeks</td>
<td>304</td>
<td>49</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN alfa -2a 3MU tiw 48 weeks</td>
<td>88</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Heathcote et al.</td>
<td>130</td>
<td>2000</td>
<td>PEG-IFN 40 kDA (180 µg/wk) 48 weeks</td>
<td>87</td>
<td>44</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN alfa -2a 6MU tiw 12 weeks then 3MU tiw 36 weeks</td>
<td>264</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Zeuzem et al.</td>
<td>132</td>
<td>2000</td>
<td>PEG IFN 40 kDA (180 µg/wk) 48 weeks</td>
<td>267</td>
<td>69</td>
<td>39</td>
</tr>
</tbody>
</table>
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Given the increased SVR rates in response to treatment with PEG-IFN, it was natural to assess the combination PEG-IFN with ribavirin as treatment for chronic HCV patients. The results of two large randomized trials are shown in table 3.

Table 3  Two randomized controlled trials with the combination PEG-IFN and ribavirin

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref. no</th>
<th>Year</th>
<th>Therapy</th>
<th>No. of patients</th>
<th>ETR %</th>
<th>SVR %</th>
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</thead>
<tbody>
<tr>
<td>Manns et al.</td>
<td>136</td>
<td>2001</td>
<td>IFN alfa-2b 3MU tiw in combination with ribavirin/day 48 wks</td>
<td>505</td>
<td>54</td>
<td>47</td>
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<td></td>
<td></td>
<td></td>
<td>PEG-IFN alfa-2b 1.5 µg/kg/wk in combination with ribavirin /day 48 wks</td>
<td>511</td>
<td>65</td>
<td>54</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IFN alfa-2b 3MU tiw in combination with ribavirin/day 48 wks</td>
<td>444</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>Fried et al.</td>
<td>137</td>
<td>2002</td>
<td>PEG-IFN alfa-2a 180 µg/wk in combination with placebo/day 48 wks</td>
<td>224</td>
<td>59</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PEG-IFN alfa-2a 180 µg/wk in combination with ribavirin /day 48 wks</td>
<td>453</td>
<td>69</td>
<td>56</td>
</tr>
</tbody>
</table>

The dose of ribavirin was 1,000 mg daily for patients with body weight less than 75 kg and 1,200 mg daily for those with body weight greater than 75 kg except in the study of Manns et al., in which patients received 800 mg ribavirin daily.

These results show that combination therapy with PEG-IFN and ribavirin was more effective than PEG-IFN alone, due to a decreased virological relapse rate. Furthermore, PEG-IFN/ribavirin combination therapy is also more effective than IFN/ribavirin combination, due to an increased ETR.

As was found in the IFN/ribavirin combination treatment schedules, SVR rates for genotype non-1 patients with 24 or 48 weeks of treatment with PEG-IFN/ribavirin were comparable. Both treatment durations showed SVR rates of almost 80%.

For genotype-1 patients the observed SVR for the 48 weeks PEG-IFN/ribavirin treatment schedule was 51%, compared to 41% for the 24 weeks schedule (133).

Treatment of chronic HCV infection: the future

Therapy for chronic HCV infection has rapidly evolved since its introduction in the early 1990s. From 5-20% eradication of the virus with IFN monotherapy to 48-88% viral eradication when using PEG-IFN with ribavirin combination therapy nowadays, chronic HCV (genotype 2/3) infection has almost become a curable disease (figure 4).
The improved outcome of therapy is impressive but above all relate to those patients who were able to tolerate therapy. Also numerous patients are excluded from treatment due to anticipated or unacceptable high risk of side effects of the IFN based therapy. Irrespective the considerable progress in the management of side effects including the use of anti-depressants to control depression and growth factors to control anemia, these issues remain considerable. Furthermore, a significant number of patients achieve a virological non-response to any currently available anti-viral treatment, even after several treatment courses. New insights in ways to interfere with the virus, the host response and the side effects of therapy are reflected in the considerable number of agents that are currently under investigation (table 6). New treatment strategies are certainly on the way(135). However, the reality is that it will take again some years before their efficacy and safety is proven and widely implemented. Till then IFN based therapy strategies will remain the therapy of choice.
Table 6  New drugs in the pipeline
Adapted from the website http://www.frontiernet.net/~monty/hcvpipel.html

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug Type</th>
<th>Development</th>
<th>Pre Clinical</th>
<th>Clinical Phase I</th>
<th>Clinical Phase II</th>
<th>Clinical Phase III</th>
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</thead>
<tbody>
<tr>
<td>Boehringer Ingelheim</td>
<td>Protease Inhibitor BILN2061</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercell</td>
<td>Therapeutic vaccine</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Viro Pharma / AHP</td>
<td>New lead</td>
<td>x</td>
<td></td>
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<tr>
<td>Isis Pharmaceutical</td>
<td>ISIS 14803 Antisense</td>
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<td>XTL</td>
<td>Monoclonal antibody</td>
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LD=lead compound development, ??=development stage unknown or drug type unknown, IND=investigational new drug application, T=terminated
General introduction

References

Chapter 1


67. Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. J Infect Dis 2001; 183(7):1112-1115.


Chapter 1


