

## CHRONIC HEPATITIS C TREATMENT: A REVIEW

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Of the seven viral hepatitis viruses so far recognized, hepatitis C virus remains the largest global challenge. For a virus positively characterized only a decade ago, it is not surprising that we are still nowhere near the elucidation of the natural history of the infection, its prevention, treatment or management. Intensive research over the past ten years continues to inundate the clinical and scientific communities with data. Achievements regarding the elucidation of genomic organization, characterization of the gene products and functions, definition of *in vivo* viral kinetics and the development of diagnostic tools for early detection of the virus have been documented. New strategies for diagnosis have improved our knowledge of the epidemiology, disease definition and progression, but when it comes to treatment and management, only a degree of uniformity exists. Effective therapy continues to elude researchers and a universal definition of sustained response to treatment has yet to emerge. This may be measured virologically (reduction of viral load or complete eradication of the virus); clinically (amelioration or reduction of symptoms); biochemically (significant reduction or normalization of liver function tests); or histologically (suppression of inflammation and prevention of progression to cirrhosis and/or hepatocellular carcinoma).

The heterogeneity and quasi-species nature of the virus and its global diversity call for local research in dealing with these issues. Challenges such as improving the low efficacy of treatment, reducing adverse reactions to current therapies, providing cheaper drugs, defining predictive factors for treatment and decreasing personal and social burdens for the patient must be addressed. Interferon (IFN) monotherapy treatment response has generally been disappointing. Combination therapy of IFN with ribavirin, however, has shown promise, at least for certain genotypes.

The new pegylated forms of IFN are promising and their combination with ribavirin may be the answer for IFN non-responders, relapsers and certain non-responsive genotypes. New hepatitis C viral infection is on the

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decrease, however, with as high as 3% of the global population already infected, the morbidity and mortality due to HCV, leading to cirrhosis and its potential complications such as hemorrhage, hepatic insufficiency, hepatocellular carcinoma and liver transplantation, will continue to dominate health budgets worldwide. Much research is warranted in the field of treatment and management.

### Epidemiology of HCV

HCV infection is a major cause of morbidity and mortality worldwide. In fact, HCV-associated end-stage liver disease is the most frequent indication for liver transplantation among adults in the U.S. As many as 200,000 patients require liver transplants every year due to HCV-related diseases, of whom 10,000 die.<sup>1</sup>

Estimates of medical and unemployment costs of HCV-related diseases amount to more than \$600 million per annum in the U.S. The WHO estimates that as many as 170 million people are infected globally. The worldwide distribution is uneven. The vast majority of infected people live in the Far East (60 million), South East Asia (32 million) and Africa (28 million).<sup>2</sup> Egypt has the highest prevalence rate among adults worldwide. The source of infection has been traced to contaminated needles used in the past for parenteral antischistosomal therapy.<sup>3</sup> Prevalence rates among the general population in developed countries are low. However, among high-risk groups such as intravenous drug addicts and hemodialysis patients the infection rates are very high. There are an estimated 8.9 million people infected in Europe and 12.6 million in both American continents, including 4 million in the US. The Middle East has a high HCV carrier rate. Based on our previous prevalence data of 2.7% (27,907 out of 1,017,303) among Saudi male blood donors, it is estimated that nearly 500,000 Saudi citizens have already been infected with the virus. In a study of 653 histologically proven chronic active hepatitis cases in the Kingdom, we found HCV in nearly 60% of the patients.<sup>4</sup> A similar study in Egypt reported HCV seropositivity of 86% among their chronic active cases.<sup>5</sup>

A recent survey among Saudi children nationwide has reported a prevalence rate of 0.2% (4 out of 1915). The

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infection rate among pregnant Saudi women in Riyadh is similarly low at 0.9% (14 out of 1509).<sup>6</sup> A notable decrease has been observed among Saudi male blood donors

nationwide. At the Riyadh Central Blood Bank, a decline from 1.3% (199 out of 15,008) in 1997, 1.2% (177 out of 15,197) in 1998 and 0.8% (126 out of 15,904) in 1999 has been documented. These results are very encouraging since there are no vaccines for the primary prevention of HCV. The decline may be largely attributed to lack of exposure through blood and its products due to sensitive screening assays, improvement in socioeconomic conditions, education and a general public awareness.

A high degree of heterogeneity exists for HCV. Currently 11 genotypes and over 90 subtypes have been identified based on the nucleotide sequence homology.<sup>7</sup> An interesting geographical and epidemiological diversity has been observed among HCV genotypes,<sup>8-10</sup> but their clinical significance remains sketchy. Whereas genotypes 1, 2 and 3 and their subtypes have a worldwide distribution and predominance in the US, Europe and Japan, others such as 4 are prevalent in the Middle East and Central Africa, 5 in South Africa and 6, principally in Hong Kong and Vietnam.<sup>11-14</sup> We have reported the predominance (74%) of genotype 4 among cases of chronic active hepatitis in Saudi Arabia.<sup>15</sup> However, there seems to be a significant emergence of subtype 1a and subtype 1b among Saudi hemodialysis patients and drug addicts, respectively. Other workers have confirmed genotype 4 predominance in the Middle East.<sup>16,17</sup> It is becoming evident that certain genotypes such as 1b and 4 show poor response to IFN treatment.

### Natural History of HCV Infection

The natural history of HCV infection, defined as the ordinary course of the disease from its inception to its resolution, is highly variable and unpredictable. In 75% of cases the infection is without symptoms. Unfortunately, in almost 90% of those infected, the infection evolves into chronicity.<sup>18</sup> Symptoms, if they occur, are usually mild, silent and progressive. However, over a period of time, in about 20% of cases, fibrosis sets in, which if unchecked can lead to cirrhosis in 20 years and hepatocellular carcinoma in 30 years.<sup>19,20</sup> Approximately 25% of these patients will develop hepatic failure or require liver transplantation. The progression to cirrhosis may be very rapid or follow a more protracted course. Several prognostic factors have been investigated and continue to be updated but to date no factor has been found to be absolutely reliable of disease progression, making it difficult to predict precisely the clinical outcomes in individual cases. These factors may be used, however, as guidelines for counseling of the patient. The age at the time of the infection, the duration of the disease, the gender, co-infection with other viruses, and the route of

infection all seem to have some influence on the natural history of the infection.<sup>21-23</sup>

Other predictors of disease progression, such as viral genotype 1b and possibly 4, baseline viral load greater than 3.5 million copies/mL, necro-inflammatory activity of the



FIGURE 1. Natural course of HCV infection.

liver, the stage of liver fibrosis and chronic alcoholism have been reported.<sup>24,25</sup>

A general model describing the natural history of HCV infection is premature. As shown in Figure 1, the tendency of HCV infection to follow a progressive clinical course from exposure to chronic active infection, cirrhosis, primary hepatocellular carcinoma or death is affected by several heterogeneous factors, some independent, others interrelated and others synergistic. The controversy rages on.

### HCV Treatment Objective

Antiviral therapy is recommended for acute and chronic HCV infections. The ultimate goal of treatment is to achieve the sustained eradication of the virus. However, this objective is difficult to attain and other parameters such as normalization of serum ALT, reduction of HCV-RNA to undetectable levels by PCR and restoration to normal histology of the liver have been considered. In the majority of cases the total eradication of the virus is not achieved. However, therapy may reduce the risk of acute cases becoming chronic and suppress the disease progression from chronic active hepatitis to cirrhosis, reducing the risk for hepatocellular carcinoma.<sup>19,26,27</sup> Long-term antiviral therapy may also minimize the chances of relapse and exacerbation of histological activity. Treatment may reduce extrahepatic manifestations and, if successful, prevent the contamination of others. There is, therefore, a strong argument to treat chronic active hepatitis (CAH) cases. There are reports that therapy may not only prevent but can reverse fibrosis.<sup>28-30</sup>

### Classification of Interferons (IFNs)

Since their discovery in 1957, both natural and recombinant alpha IFNs have been shown to have bioactivity that interferes directly or indirectly with viral reproduction at both biochemical and cellular levels.<sup>31</sup> They have been shown to have immunomodulatory and

antiproliferative properties as well. IFN can improve hepatic inflammation, reduce viral replication and normalize LFTs in HCV patients.

Interferons are classified broadly as alpha (derived from monocytes and transformed B-lymphocytes), beta (produced from fibroblasts) and gamma (produced by activated T-helper lymphocytes). Although several forms have been isolated, only four, namely IFN-alpha 2a, IFN-alpha 2b, consensus IFN and lymphoblastoid IFN, are commercially available and approved for the treatment of viral hepatitis. The IFN-alpha 2 gene has been cloned and inserted into bacteria. This has led to the production of recombinant IFN-alpha 2, which is marketed as Roferon<sup>®</sup> (IFN-alpha 2a) and Intron<sup>®</sup> (IFN-alpha 2b). The two recombinant IFNs differ by only one amino acid residue.

In the past, IFN has been used in the treatment of chronic HBV with a nearly 40% response rate but lately, Lamivudine has been preferred. In cases of chronic HCV infections, IFN monotherapy results in only a 10%-20% sustained response rate.<sup>32-34</sup> Although about 40% of patients achieve response at the end of treatment, patients relapse in almost 50% of cases. Viral genotypes 1b and 4 infections seem to be poorly responsive to IFN treatment<sup>16,35</sup> compared to genotypes 1a, 2 and 3.<sup>36-38</sup>

Ribavirin (1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide), a synthetic broad-spectrum guanosine-like nucleoside, has been found to have inhibitory actions *in vitro* against a wide range of DNA and RNA viruses.<sup>39,40</sup> Its mode of action is thought to include the inhibition of inosine 5' monophosphate dehydrogenase,<sup>41</sup> inhibition of viral replication by interfering with RNA polymerase modulation of immune response by alteration of the levels of Th-1 and Th-2 cells and direct cytoprotection leading to decrease of hepatic inflammation.

The drug has been used in an aerosol formulation to treat influenzae A and B viruses and respiratory syncytial virus infections. Ribavirin marketed as Rebetol<sup>®</sup> in the treatment of chronic HCV infection has been attempted but with a rather poor response rate.<sup>42,43</sup> In certain cases, beneficial effects on biochemical levels such as reduction of serum aminotransferases and improvement of liver histology such as hepatocellular necrosis and inflammation but not fibrosis have been reported.<sup>44,45</sup> However, ribavirin monotherapy is not associated with a significant reduction in HCV-RNA levels, bringing into doubt if the drug has any antiviral effect.<sup>44-47</sup> The reported beneficial effects are not sustained after the end of therapy and all hepatitis C patients treated with ribavirin monotherapy relapse. It is, therefore, the synergistic effect of the ribavirin and IFN that provides the advantages of combination therapy, and IFN monotherapy is being superseded by combination therapy with ribavirin in the treatment of chronic hepatitis C.

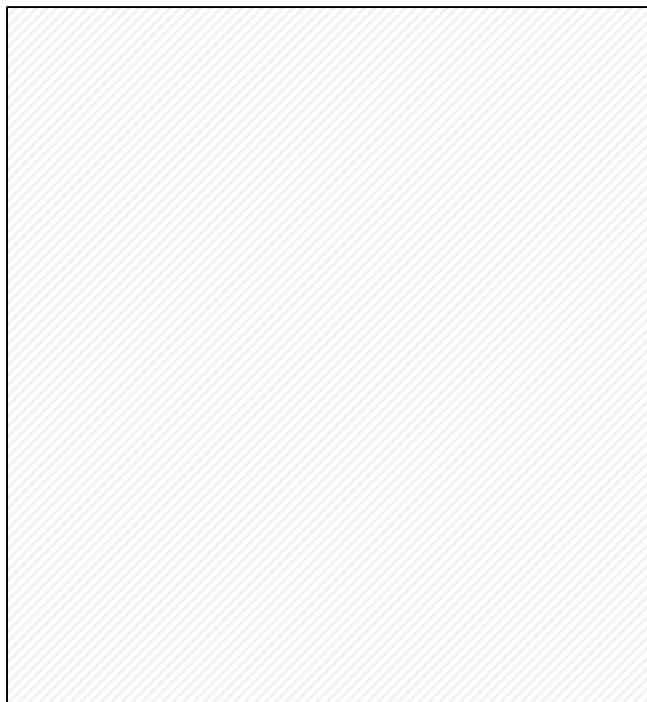


FIGURE 2. Algorithm for diagnosis and management of chronic hepatitis C.

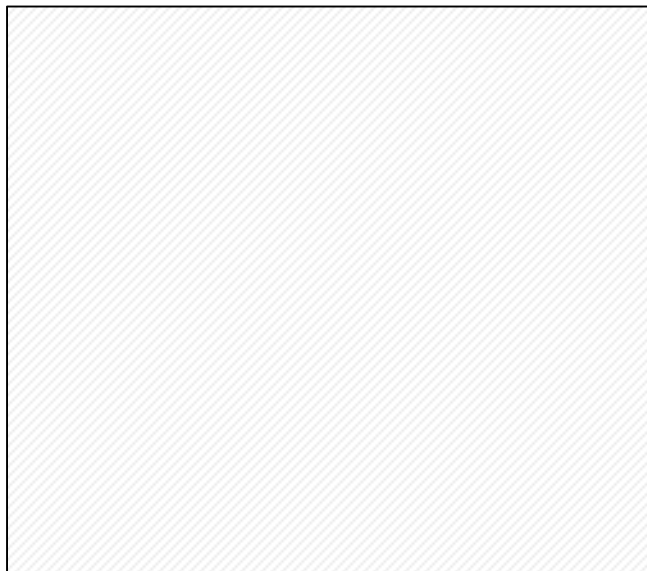


FIGURE 3. Algorithm for treatment of chronic hepatitis C.

### Combination Therapy: IFN Plus Ribavirin

The combination of IFN with ribavirin in the treatment of chronic hepatitis C has yielded a more effective virological and histological response compared to monotherapy using either drug.<sup>46-48</sup> Results of three large multicenter randomized trials have shown that combination therapy increases end-of-treatment response significantly and, most importantly, sustained response.<sup>46,47,49</sup> Although large clinical trials for combination therapy for genotype 4 patients are lacking, El-Zayadi et al. treated 26 HCV genotype 4 Egyptians with combination therapy and reported a significant biochemical but not virologically sustained response.<sup>50</sup> In a recent study, Al Faleh et al. reported a disappointing response rate of only 5% among Saudi genotype 4 CAH patients.<sup>51</sup> Although preliminary, these results may emphasize the role of HCV genotypes even with combination therapy.

There is an urgent need for new therapies and treatment modalities for genotype 4 chronic HCV patients. In the patients with positive demographic criteria, treatment with combination therapy for 12 months may lead to a higher favorable sustained response. Combination therapy is, therefore, becoming the optimal option of treatment for patients of chronic hepatitis C, especially for patients with favorable prognostic factors. It is the most efficacious treatment to date and is becoming the first line of treatment in naive patients and those who relapse after IFN monotherapy. In nonresponders to IFN monotherapy, combination therapy has been found to increase sustained response rate and reduce the relapse rate.<sup>52,53</sup> However, patients with contraindications for ribavirin must continue to be treated with IFN alone. The optimal duration for combination therapy is 6 months for genotypes 1a, 2 and 3, but 12 months for genotypes 1b and 4.

Ribavirin dosage approved for combination therapy with IFN is 1000 to 1200 mg in split daily doses, orally with food, depending on body weight. Patients with body weight less than 75 kg may be given up to 1000 mg, whereas those with body weight above 75 kg can be given 1200 mg daily. Anemia may occur and may be managed by reduction of dosage up to 600 mg/day.

### Pegylated Interferon Alpha

Hoffman-La Roche (Switzerland) and Schering-Plough (U.S.A.) have recently developed a new generation of IFN by covalently linking a branched methoxy polyethylene glycol moiety to IFN. These new drugs (Pegasys<sup>®</sup> and PegIntron<sup>®</sup>) have been found to have a decreased systemic clearance rate, improving the serum half-life by ten-fold without altering the properties of the parent compound. Their biological activity, as measured using serum 2,5-oligoadenylate synthetase activity (OAS), is prolonged.<sup>53,54</sup>

The outcomes of recent phase II trials showed a 76% virologic response at the end of a 12-week treatment and a sustained response rate of nearly 40% with Pegasys.<sup>55</sup> Again, the response seems to be genotype dependent, since 28% of those infected with genotype 1 and 56% of genotype 2 and 3 attained sustained response. Clinical studies with PegIntron have reported a 25% virological sustained response. Pharmacodynamic (PD) and pharmacokinetic (PK) profiles of the new drug are improved compared to IFN, and preliminary studies have shown that PEG-IFN injected once a week is more efficacious than IFN injected thrice weekly.<sup>56</sup> The new pegylated interferons are into phase III clinical trials and are expected to be available commercially in the near future. The above preliminary results suggest that the combination of PEG-IFN with ribavirin may be more effective than IFN plus ribavirin. Clinical trials using PEG-IFN and ribavirin have started worldwide.

### Dosage and Side Effects

Ideally, IFN either as a monotherapy or in combination with ribavirin must lead to a low host toxicity and high viral clearance rate. Many studies have assessed the impact of different treatment schedules, responses and side effects. Three main regimens, namely, longer duration therapy, higher fixed doses and intensive dose induction, have been applied. Patients with favorable predictive factors of response, such as short duration of the disease, viral genotypes 2 and 3, low viral load, absence of fibrosis and cirrhosis, may respond to a standard combination regimen for six months,<sup>57</sup> but this must not be considered as a rule since other factors such as age and sex may play an important role. On the other hand, those with high viral load, genotypes 1b and 4, longer duration of disease, presence of fibrosis and compensated cirrhosis may require higher-dose regimens and longer treatment duration<sup>58,59</sup> of 48 weeks to reduce relapse and obtain improved sustained response. Generally, high doses are associated with more adverse reactions and patients must be well monitored.

Induction dosing, in which one large dose or more frequent doses are applied at the beginning of treatment, has been attempted, especially among IFN non-responders and relapsers, but it is still too early to predict its effectiveness.

A variety of side effects are associated with IFN monotherapy. Influenza-like symptoms such as fever, headache, fatigue, arthralgias and myalgias predominate in nearly 60% of patients at the early stage of treatment.<sup>47</sup> These symptoms are well tolerated in many patients and can be ameliorated by acetaminophen. Severe adverse events such as depression, suicidal ideation, suicide and hypothyroidia, though uncommon, should not be ignored and may require dose modification or discontinuation of therapy. Other adverse events such as pharyngitis,

insomnia, dyspnea, pruritus and nausea are less frequent and may be managed by dose reduction.

Side effects associated with PEG-IFN are usually mild to moderate, similar to those of IFN monotherapy and manageable with dose adjustment. The symptoms appear to decrease in severity as treatment continues.

Ribavirin is associated with major side effects, such as anemia due to extracellular hemolysis and suppression of bone marrow release of erythroid elements.<sup>41</sup> The anemia usually reaches its nadir within the first four weeks of treatment. Anemic HCV patients must therefore be excluded from ribavirin treatment. Regular monitoring of hematological indices is warranted, especially during the first 4 weeks of treatment. Lymphopenia, gastrointestinal complaints and CNS defects have also been implicated.<sup>42</sup> If hemoglobin concentration falls to lower than 10 g/dL, dosage must be reduced by 50%. Reduction of hemoglobin to below 8 g/dL should lead to cessation of treatment. The drug is teratogenic and strict attention to birth control is warranted in women of childbearing age throughout the treatment period and six months after.

Men on ribavirin combination treatment must use barrier contraceptives (e.g., condom) throughout the treatment and post-treatment periods since the drug can be transmitted through semen.

### To Treat or Not to Treat

The question of whether to treat or not to treat depends on many factors. The decision should be made not only on clinical grounds but social and economic as well. Not all HCV infection leads to disease. The disease is characteristically slowly progressive, taking years if not decades to manifest. Large-scale prospective natural history data comparing treated and untreated patients are lacking. The present consensus is to treat not the infection but the disease. Patients with symptoms whose liver biopsies confirm features of moderate to severe degree of necroinflammatory activity (grade) and fibrosis (stage) or those in the early phase of compensated liver cirrhosis must be treated as shown in Figure 2.<sup>60,61</sup> Healthy HCV carriers with negative HCV-RNA, minimal grade of necroinflammation (A0) or minimal fibrosis (F0) must be monitored but not treated. However, healthy HCV carriers with persistent HCV-RNA, but low Histological Activity Index may benefit from the delay of the speed of progression to fibrosis if treated.

Patients whose cirrhosis is more advanced and/or decompensated or who have hepatocellular carcinoma or end-stage liver disease do not seem to benefit from treatment and must be considered for liver transplantation if they are found to be suitable.

In our predominantly genotype 4 region, combination therapy must be the first line of treatment, since IFN monotherapy has a low sustained response rate among our

patients and despite the poor response rate reported from a few preliminary studies in the region.

It is imperative that all treatment is carefully monitored biochemically, histologically and virologically throughout the therapy phase, as shown in Figure 3. Pre-treatment quantitative HCV-RNA baseline must be established. A second sample taken 24 weeks post-treatment must be analyzed for quantitative HCV-RNA. In the patients showing no significant reduction of the HCV-RNA, it may be necessary to change the treatment dosage, try pegylated-IFN, or drop them from the treatment scheme.

### Future Trends for HCV Treatment

Innogenetics (Belgium) has started a Phase I Clinical Study using a therapeutic hepatitis C vaccine capable of stimulating the immune system to produce antibodies that not only prevent primary infection but also eliminate the virus in HCV carriers. Results in human volunteers will be available in December 2000 and are eagerly awaited.

Several agents, such as ursodeoxycholic acid, N-acetylcysteine, NSAIDs and others, have been proposed as adjuncts to IFN treatment, but none have been shown to be of significant benefit. Several researchers are of the notion that multidrug approaches, as with HIV treatment experience, may be our best prospects. New drugs such as amantadine/rimantadine, protease/helicase/polymerase inhibitors and antisense oligonucleotides are being actively pursued and the design of specific inhibitors, similar to those used for HIV treatment, are in the offing. However, the virus is very heterogeneous with a high mutation rate. Drug resistance will be expected in the future.

Triple therapy of IFN, ribavirin and amantadine has been attempted on nonresponders, but the results are still awaited.

### Conclusion

In conclusion, whereas public health measures may be successful in preventing new infections, treatment will continue to be an option for old infections. For HCV chronic carriers without symptoms, regular monitoring of liver functions and periodic measurement of HCV-RNA should suffice. No treatment is necessary in this group. For chronic HCV carriers with symptoms such as chronic active hepatitis and compensated liver cirrhosis, combination therapy must be considered. However, the present treatment regimens are still experimental, with poor sustained responses, and are expensive and not without side effects. Patients contemplating treatment must be fully aware of the need for frequent hospital visits, strict compliance to drug regimens and long-term monitoring.

Treatment without monitoring is fruitless and wasteful. Specialized referral centers with facilities for biochemical, virological and histological monitoring must supervise all treatment. Combination therapy of IFN and ribavirin is

becoming the standard treatment but this may not be the case for genotype 4 CAH patients if preliminary reports of poor responses are confirmed with larger studies. For non-responders and relapsers, more potent antiviral drugs and their combinations are the likely direction in the future. Our region is predominantly genotype 4 and, as such, results of clinical trials in Europe and the US, based on different genotypes, may not be extrapolated and assumed to be of benefit. The new pegylated interferons may be used in combination with ribavirin in clinical trials into genotype 4 patients. We are hopeful that future clinical trials in this region will be given the support they truly deserve. Hepatitis C as a disease will continue to persist, and so will the challenge to combat the infection by combination therapy.

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