Historical treatment of chronic hepatitis B and chronic hepatitis C

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Abstract
Interferon is currently considered to be the only accepted effective treatment for chronic viral hepatitis. A history of the treatment of chronic hepatitis B and C before the use of interferon is presented here. Hepatitis B virus does not seem to be directly cytopathic and the disease is known to be modulated largely by the host’s immune response. Experience with immunosuppressant and immunostimulant drugs and a wide variety of antiviral agents, however, has indicated that none of these are of any benefit in patients with chronic hepatitis B, with the possible exception of adenine arabinoside. In view of the much more recent identification of the hepatitis C virus, studies of therapy for chronic hepatitis C are inevitably less extensive. A pilot study using acyclovir in patients with chronic non-A, non-B hepatitis did not show any benefit, although the treatment period may have been too short for the results to be conclusive. The only agent other than alpha interferon to be tried in chronic hepatitis C is ribavirin, which may have some activity. Many of the agents studied in chronic hepatitis B should also be investigated for the treatment of patients with chronic hepatitis C.

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In reviewing the history of the treatment of chronic viral hepatitis one has to keep in mind that treatment of any disease depends on a precise understanding of pathogenetic mechanisms and the availability of drugs able to interfere with these. As with other diseases, there has been an explosion in knowledge on viral hepatitis within the past two decades. Landmarks in the development of current pathogenetic concepts and understanding of the viral aetiology of chronic hepatitis are summarised in Table I. Before identification of the various hepatitis viruses and the development of precise diagnostic techniques, treatment of viral hepatitis with a wide variety of drugs was empirical. Their mode of action was poorly defined and their effects were not proved by valid, randomised controlled studies. Furthermore, studies may have included patients with liver diseases of different aetiologies, which means they cannot be compared with therapeutic trials conducted currently. The history of treatment of chronic hepatitis starts with the discovery of the hepatitis B virus (HBV). A wide variety of drugs with established benefit in the treatment of other chronic diseases, or with known antiviral effects towards other viruses, were screened for their potential to influence the course of chronic viral hepatitis. Most of these drugs were tested only in small pilot trials which may have been insufficient to detect efficacy. This overview considers these efforts, excluding the development of interferon treatment, which was first used for the treatment of chronic hepatitis B in 1976.1 Today, interferon is considered to be the only accepted effective treatment for chronic viral hepatitis.

Treatment of chronic hepatitis B
The discovery of HBV in 19672 and the subsequent development of useful diagnostic tests facilitated the study of both the natural history of chronic viral hepatitis B and of the pathogenetic factors contributing to its progression. HBV is not directly cytopathic, and immune mechanisms are important in both the persistence of, and recovery from, HBV infection. Eradication of infected hepatocytes is mediated by cytotoxic T cell lysis. Chronic hepatitis may result from an inadequate immune response to HBV. Thus, treatment is aimed at modulation of the immune response (by suppression or stimulation) or inhibition of viral replication.

IMMUNOMODULATION
Immunosuppression
It was assumed that immunosuppressant drugs might be of value in the treatment of chronic active hepatitis, given their beneficial effects in autoimmune chronic active hepatitis.

### TABLE I  Landmarks in viral hepatitis

| What is hepatitis? |  |
|--------------------|--|---|
| Hippocrates |  |
| Virchow (1865) |  |
| 1940s |  |

| What causes hepatitis? |  |
|------------------------|--|---|
| Viral hepatitis: |  |
| Epidemic studies in the 1940s and 1950s |  |
| 1965-1967 | - two types of virus - discovery of HBSAg by Blumberg - hepatitis A virus (Fenstrome) - delta-agent (Rizzetto) - hepatitis C virus (Houghton et al.) - hepatitis E virus (Krawczinski) - autoimmune hepatitis (Waldenstrom, MacKay) - Wilson’s disease (Sternlieb) - drug induced hepatitis |
| 1973 |  |
| 1977 |  |
| 1987-1989 |  |
| 1989 |  |

| Non-viral hepatitis: |  |
|---------------------|--|---|
| 1950-1956 |  |
| 1972 |  |
| 1976s |  |
Corticosteroids. Corticosteroids were the first drugs to be used for the treatment of chronic hepatitis in the 1950s. Three controlled trials were conducted in patients with chronic active hepatitis in the 1960s, and although at this time an aetiological classification of chronic hepatitis was not possible, all three showed an improvement in survival after treatment with corticosteroids. Further analysis of these studies showed that most patients had autoimmune hepatitis, but about 10% were found to be hepatitis B surface antigen (HBsAg) positive. These patients did not respond as well to steroid treatment as the patients who were HBsAg negative. Subsequent controlled trials in patients with chronic hepatitis B indicated that steroid treatment was not only ineffective but even detrimental. The reason for the poor response of chronic hepatitis B to steroids may be partly explained by an increase in viral replication. Spontaneous seroconversion of hepatitis B e antigen (HBeAg) to anti-HBe positivity and disappearance of HBV-DNA occurs less frequently in steroid treated patients than in placebo treated or untreated patients (15% per year). Stopping steroid treatment usually leads to a rebound in hepatic disease activity but may be followed by termination of viral replication within a few months. Thus, despite the decrease in transaminase activity, steroids have no beneficial (and sometimes a detrimental) effect on liver histology, morbidity, and mortality, and should not be used for the treatment of chronic hepatitis. Their only role may be the enhancement of the efficacy of interferon or adenine arabinoside (ARA-A) treatment by prior steroid withdrawal in patients with mild inflammatory activity.

Other immunosuppressive drugs. Other immunosuppressive agents such as azathioprine or 6-mercaptopurine were not better than placebo in the treatment of chronic hepatitis, but in combination with steroids exerted a steroid sparing effect.

Immunostimulation

Hepatocytes containing replicating or integrated HBV are destroyed by cytotoxic T cells that recognise foreign or changed liver membrane determinants. An ineffective immune response may be one of the key factors responsible for development of chronic hepatitis B. Therefore, in chronically infected subjects, various immunostimulants listed in Table II have been used to assist the immune system in clearing infected cells. Most of these compounds were tested in only a small number of patients and produced few beneficial effects. Immunostimulation with repeated intradermal applications of Bacillus Calmette Guérin (BCG) was followed by disappearance of HBsAg in a few patients, but these findings were not confirmed by others.

A drug of potential interest is levamisole which produces increased T cell concentrations, and therefore induces non-specific immune stimulation. Short term treatment has led to an increased destruction of infected cells but all patients have remained HBsAg positive. Chronic treatment with levamisole has resulted in a higher rate of HBV-DNA elimination and HBeAg-anti-HBe seroconversion than that found in placebo treated patients. These data await confirmation by other randomised, controlled trials in a larger group of patients.

Immunomodulation by cytokines

An improved understanding of the control of the immune response by humoral factors, and the synthesis of these compounds by recombinant gene technology, may allow a more targeted enhancement of the immune response with cytokines such as interleukin-2, tumour necrosis factor (TNF), or interferon gamma in patients with chronic hepatitis B. Interleukin-2 causes cytotoxic T cells to mature and increase in number and may thereby enhance elimination of infected hepatocytes. An open study in 11 patients suggested that it may be beneficial for the treatment of chronic hepatitis B, although these results need confirmation by randomised, controlled studies. Interferon gamma, which has low antiviral activity, enhanced the effects of interferon beta in chronic hepatitis, probably as a result of its immunomodulatory properties. Tumour necrosis factor is an immunoregulatory cytokine with antiviral properties. Its effect in chronic HBV infection is complex and cannot be explained by its antiviral properties. A clinical study has shown that HBV replication is inhibited by low doses of tumour necrosis factor but increased by higher doses.

ANTIVIRAL TREATMENT

A variety of antiviral drugs inhibit HBV-DNA production in vitro. Those that have been tested in patients with chronic hepatitis B are listed in Table III.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Introduced</th>
<th>Efficacy</th>
<th>Anecdotal</th>
<th>Randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levamisole</td>
<td>1974</td>
<td>+</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>Transfer factor</td>
<td>1976</td>
<td>-</td>
<td>-</td>
<td>ND</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>1973</td>
<td>-</td>
<td>-</td>
<td>ND</td>
</tr>
<tr>
<td>Freund's adjuvant</td>
<td>1977</td>
<td>+</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>BCG</td>
<td>1978</td>
<td>+/-</td>
<td>+/-</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not determined, +: effective, -: no effect, +/-: conflicting data.
Historical treatment of chronic hepatitis B and C

<table>
<thead>
<tr>
<th>Substance</th>
<th>Introduced</th>
<th>Efficacy In vitro</th>
<th>Randomised controlled trial</th>
<th>Anecdotal</th>
<th>Major toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARA-A</td>
<td>1976</td>
<td>+</td>
<td>+/-</td>
<td></td>
<td>Neurmuscular</td>
</tr>
<tr>
<td>ARA-AMP</td>
<td>1984</td>
<td>+</td>
<td>+/–</td>
<td></td>
<td>Neuromuscular</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>1981</td>
<td>+</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foscarnet</td>
<td>1986</td>
<td>+</td>
<td>ND</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Suramin</td>
<td>1987</td>
<td>+/-</td>
<td>ND</td>
<td>–</td>
<td>Liver failure</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>1988</td>
<td>+</td>
<td>ND</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td>1978</td>
<td>+</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phyllanthus amarus</td>
<td>1987</td>
<td>+</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon alfa</td>
<td>1976</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ND = not determined, *=effective, – = no effect, +/- = conflicting data, ? = not clear or incomplete data available.

ARA-A = adenine arabinoside; ARA-AMP = adenine arabinoside monophosphate.

Selected more potently against viral than against mammalian cell polymerase. ARA-A must be administered by slow intravenous infusion, while ARA-AMP can also be given intramuscularly. Both compounds have a robust antiviral activity (including an effect on HBV-DNA), both in vivo and in vitro. ARA-A was first used for the treatment of chronic hepatitis B in 1978. Since then, the results of controlled trials with ARA-A or ARA-AMP have been conflicting. Studies from the USA failed to show a benefit of treatment, while European trials demonstrated an increased HBeAg-anti-HBe seroconversion rate with ARA-A or ARA-AMP. A meta-analysis based on the eight published randomised, controlled trials calculated an overall odds ratio for HBeAg seroconversion of 2.37 for ARA-A/ARA-AMP therapy.

Side effects with ARA-A are common and dose related. The most relevant clinical side effect is neuromuscular toxicity, which is associated with severe pains mainly in the paravertebral and lower limb muscles. Combination with human leukocyte interferon has been shown to enhance toxicity and does not improve the overall efficacy.

Acyclovir and descyclovir

Acyclovir and descyclovir, the oral pro-drugs, are non-cyclic guanosine analogues that specifically inhibit viral but not host cell DNA synthesis. They inhibit DNA polymerase activity in Peking ducks infected with hepatitis B. Two small, randomised controlled studies have been performed in patients with chronic hepatitis B, where acyclovir showed transient inhibition of HBV replication but no significant effect on the HBeAg seroconversion rate. The enhancement of the antiviral effects of alpha lymphoblastoid interferon by acyclovir and possibly by descyclovir has to be confirmed by appropriate trials.

3'-azido-3'deoxythymidine (Zidovudine) and Suramin

Since reverse transcriptase activity is a prerequisite for HBV replication, inhibitors of reverse transcriptase may be useful for the treatment of hepatitis B. Zidovudine and suramin (a drug used for the treatment of trypanosomiasis) inhibit HBV replication in vitro. Zidovudine has decreased HBV replication in patients with hepatitis B.

Triodiod-phosphonofomate (Foscarnet)

Foscarnet inhibits HBV-DNA polymerase in vitro and has been administered to a few patients with fulminant hepatic failure due to hepatitis B. It appeared to decrease mortality in these patients and, in the largest study, six of eight patients survived. No reports are available on the potential effects of this drug in patients with chronic hepatitis B.

Extract of Phyllanthus niruri (amarus)

An extract of this plant had been used traditionally in southern India to treat jaundice, and has been shown to inhibit viral replication in woodchuck hepatitis. In a randomised, placebo-controlled study using the dried, powdered, and sterilised plant, high rates of HBeAg seroconversion were observed. No serious side effects were reported. However, only incomplete follow up data were available.

Ribavirin

Ribavirin is a nucleotide analogue which inhibits the in vitro synthesis of DNA. In a short-term trial, ribavirin failed to decrease HBV-DNA polymerase activity or HBeAg concentrations, and had no effect on liver function in six HBeAg positive patients. In the light of the apparent beneficial effects of this drug in chronic hepatitis C, it has recently been re-evaluated in the treatment of hepatitis B, and now seems to be effective (Fried et al abstract presented at the Annual Meeting of the American Gastroenterological Association, San Francisco, 1992).

Other Drugs Used for Treatment of Chronic Hepatitis B

D-penicillamine

D-penicillamine, a chelating agent, is the treatment of choice in patients with Wilson's disease. It has also been used in primary biliary cirrhosis. In addition to its copper-chelating actions, it has anti-inflammatory properties and may stimulate fibre removal from the liver. It has been tried successfully in some patients with chronic hepatitis but not in controlled trials.

Hepatoprotective agents

Hepatoprotective agents are substances which are able to prevent toxic liver cell injury. They are used widely in Europe for the treatment of a variety of liver diseases. (+)-Cyanidanol-3, a flavoid extracted from the plant Uncaria gambir, was tested in a large, double blind study involving 338 HBeAg positive patients.
It was found to enhance the HBcAg sero-conversion rate after 14 weeks of treatment.34 However, in another controlled trial which included various forms of chronic active hepatitis, no effects of this drug were observed in HBsAg-positive patients.35 Similarly, subgroup analysis of a large, placebo-controlled prospective trial in patients with various forms of liver cirrhosis, indicated that silymarin, an extract from the milk thistle fruit, Silybum marianum Gaertner, L, did not affect the outcome of HBsAg positive patients.36

32 Thayagarajan SP, Subramanian S, Thirunalassundari T, et al. Effect of Phyllanthus amarus on chronic carriers of
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