THE TREATMENT OF VIRAL HEPATITIS: A REVIEW

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HEPATITIS B INFECTION

INTRODUCTION

Hepatitis B infection (HBV) affects 300 million people in the world, most of whom (75%) are Asian. It is one of the major causes of mortality and morbidity. The spontaneous remission rate for untreated HBV infection is approximately 80%, but the likelihood of chronic hepatitis approaches 90% if patients are infected early in life.

PROGNOSTIC INDICATORS

The favourable prognostic indicators for **interferon** therapy are

- high alanine aminotransferases (ALT)
- low HBV DNA titre
- short duration of infection, no immune suppression
- no liver decompensation
- no HIV co-infection.

ESTABLISHED TREATMENT

Interferon

Currently, **interferon** is the only licensed treatment available for patients with HBV infection. The aim of the treatment is to achieve Hbe seroconversion so as to prevent cirrhosis and hepatocellular carcinoma, reduce transplant rate and increase survival. Results of **interferon** on HBV infection have been relatively disappointing so far, with loss of HbeAg and HBV DNA only 20% higher than controls, and loss of HBSAg 5-6% higher.

In fact there has been some doubt over the efficacy of **interferon** therapy by AA Evans⁽¹⁾ and co-workers, as they reported a high spontaneous loss of HbeAg among American-Asians prospectively followed over 25 months in a hepatoma screening trial. They calculated that more than 90% of HBV carriers infected at birth would seroconvert to HbeAg negative at the age of 50. The overall spontaneous remission rate was 15-23%, and they concluded that **interferon** would only enhance HbeAg loss by 8-18 months. However, trials on European populations showed a spontaneous seroconversion rate of only 9% over 15 months, a figure quite at odds with Evans. Also, a long-term follow-up (105 months) on Chinese patients showed that patients treated with **interferon** maintained a HbeAg seroconversion rate 10-20% higher than the untreated group.

OTHER TREATMENTS

An agent that has been extensively studied in the context of hepatitis B treatment is **Lamivudine**. It is an oral nucleoside analogue which inhibits DNA replication and improves serum ALT and hepatic histology in the majority of patients. This is very encouraging but unfortunately most patients relapse when treatment is discontinued. The emergence of resistant species has been reported in patients treated with **Lamivudine** (14%), and with **Famciclovir**. However, these **Famciclovir**-resistant and **Lamivudine**-resistant HBV mutants remain susceptible to **Adefovir**, which so far has not been found to engender resistant mutations in HBV infection.

The results of **steroid** priming followed by **interferon** therapy were quite encouraging, especially in patients with minimal liver disease and those acquiring the disease at birth. Krogsgaard *et al*⁽²⁾ studied 213 patients treated with a reducing dose of **prednisolone** over a four-week period followed by **interferon** therapy, and showed a HbeAg disappearance rate of 44%, compared to 28% in the placebo group. HBSAg became negative in 15%.

INTERFERON, HBV AND HEPATOCELLULAR CARCINOMA

Hepatitis B infection is a risk factor for hepatocellular carcinoma (HCC) in patients with chronic liver disease. **Interferon** was found to decrease hepatocellular carcinogenesis in patients with cirrhosis caused by HBV. The cumulative occurrence of HCC in one study⁽³⁾ was 4.3% (treated with **interferon**) versus 13.3% (no treatment) at three years, 7.0% vs 19.6% at five years and 17% vs 30.8% at ten years.

HEPATITIS B INFECTION AND LIVER TRANSPLANT

HBV cirrhosis is one of the main indications for liver transplantation. It is contraindicated if there is any evidence of replicating virus, because recurrence is almost universal (80% in the absence of prophylaxis). The risk of hepatitis B re-infection is higher in patients with chronic liver disease, in HBV-related liver disease alone rather than in those with HBV-hepatitis delta virus HDV infection. HB immunoglobulin has been shown to reduce HBV recurrence to 30% in patients on longterm treatment. Patients with HBV-HDV liver disease receiving immunoprophylaxis are at low risk of HBV recurrence (10-15%). HDV recurrence is higher at 80% but this is of no clinico-pathological consequence in the absence of concomitant HBV re-infection.

Grellier *et al*⁽⁴⁾ examined the efficacy of **Lamuvudine** in HBV re-infection in liver transplantation for HBV cirrhosis.

Lamivudine 100mg was given to 12 patients for four weeks before transplant and for 12 months after. Only one patient had recurrence of HBV DNA at 72 weeks with histological evidence. Nine patients had clearance of HBV DNA and HbsAg at 24 weeks. This is promising but there are still unresolved issues. It is difficult to know how long to continue **Lamivudine**. Unnecessarily prolonged treatment is associated with the emergence of YMDD variant of the HBV resistant to treatment. A 27% appearance rate of resistant variant has been reported after a 12-month treatment of **Lamivudine** post liver transplant.

CONCLUSION

Clearly, better treatment options are required. As has become obvious from the experience with the treatment of HIV, the future of HBV treatment may be in combination therapy; in particular, drugs with different modes of actions, different toxicity and maximal reduction in viral replication.

HEPATITIS C VIRUS

INTRODUCTION

Hepatitis C infection (HCV) affects 0.01-1.0% of the population in the UK and northern Europe, 1-5% in southern Europe and up to 20% in the Middle East, particularly Egypt. Generally, progression to cirrhosis is slow but 85% of the cases will eventually develop chronic disease. Thirty percent of those with chronic hepatitis C will go on to develop cirrhosis. Eighteen percent of the cirrhotic patients will develop hepatocellular carcinoma (HCC) over 20 months.

INDICATIONS FOR INTERFERON TREATMENT

Most acute hepatitis C infections are silent. The current indications for **interferon** treatment are:

- raised ALT
- anti-HCV in the serum
- chronic hepatitis on histology.

Liver biopsy is essential before treatment. Histology provides information about the extent and distribution of inflammation, and allows grading and staging of the disease. Polymerase chain reaction testing (PCR) for hepatitis C is vital as it provides information for the requirement for treatment and also the infectivity. Patients with PCR-positive hepatitis C virus are at an increased risk of transmission of their disease. The risk is minimal, however, in those who are PCR negative. This is proven in a systematic review from Australia⁽⁵⁾ on 2022 patients where no definite cases of transmission were reported among the 874 patients exposed (vertical exposure, blood transfusion and needle stick injury) to sources positive for HCV antibodies and PCR negative. However, 148 cases of the 1148 patients exposed to sources positive for HCV antibody and PCR positive were infected. This has important implications as patients can be advised accordingly regarding their infectivity.

No treatment is currently recommended for patients with normal liver function tests. Several studies looking at **interferon** therapy in patients with hepatitis C and normal ALT showed no sustained virological and histological response. Flare-up of ALT has also been observed in up to two-thirds of patients.

PREDICTORS OF RESPONSE

Several indicators for good responders have been identified. These include:

- a young patient with normal gamma GT
- grade 0 to 1 steatosis and fibrosis
- low viral titre
- infection with genotype 2a and 3a.

The best predictor for treatment response is early normalisation of ALT. Failure to clear HCV RNA after a month of treatment is strongly and independently associated with a low probability of a sustained response to **interferon**. Other measures that have been examined are serum iron level, liver iron concentration, serum vitronectin level, haemosiderin deposits in portal endothelial cells and interferon receptors but results are inconclusive and they would need to be confirmed in a larger prospective study.

ESTABLISHED TREATMENT

Interferon is the treatment of choice at present. The currently recommended therapy of chronic hepatitis C is a 12-18 month course of **alpha interferon** in doses of three million units three times a week. This regimen has resulted in a sustained response rate of 20% in patients. A higher dosage and longer duration of treatment have been tried on non-responders and relapsers but failed to make a significant impact in inducing sustained response. They were also found to have more side effects.

The most promising combination therapy has been **interferon** and **ribavirin**. McHutchinson *et al*⁽⁶⁾ showed a sustained response rate of 38% with a combination therapy for 48 weeks as an initial treatment in patients with chronic hepatitis C. Treatment for 24 weeks was associated with a sustained response of 31% (combination group) vs 6% (**interferon** alone). The combination therapy had also been shown to be effective in relapsers of chronic hepatitis C. Davis *et al*⁽⁷⁾ found a sustained response rate of 49% (combination group) vs 5% (**interferon** alone) 24 weeks after treatment cessation. HCV RNA levels of two million copies or fewer were associated with a higher rate of sustained response.

This combination therapy may also have a role in those who have failed a standard course of **interferon** therapy. In a randomised controlled trial of four hundred patients with chronic hepatitis C, Barbaro *et al*⁽⁸⁾ found a sustained response rate of 14% among the previous non-responders and 30% among the relapsers at 24-week follow-up in the group treated with a combination of **interferon** and **ribavirin**, compared to 1% of non-responders and 5% of the relapsers treated with **interferon** alone. Favourable results have also been reported by others.

OTHER TREATMENTS

Ursodeoxycholic acid has been shown to improve serum ALT levels to within normal limits after cessation of **interferon** therapy. However, it has no effect on viraemia or histology. Thymosin alpha-1 was not effective when used alone, but when used in combination with **interferon** it improved biochemical, virological and histological parameters. Similarly, when used alone, **amantadine** significantly reduced serum ALT without much effect on viraemia.

However, a combination therapy may be very useful especially in **interferon** non-responders. In a pilot study by Brillanti *et al*⁽⁹⁾ a triple therapy using **interferon**, **ribavirin** and **amantadine** was superior when compared with **interferon** and **ribavirin** in patients who had previously failed to respond to **interferon** therapy alone. This combination seems promising and should be confirmed in a larger prospective trial.

Other potentially useful treatments are recombinant human granulocyte colony-stimulating factor plus **interferon**. **Cyclosporin** has also been studied but results were disappointing.

INTERFERON, HEPATITIS C VIRUS AND HEPATOCELLULAR CARCINOMA

Interferon therapy is currently not indicated in patients with cirrhosis as the response rate is poor. However, treatment in this group of patients has been associated with an improved mortality and morbidity. The risk of developing HCC is also reduced. Kasahara *et al*⁽¹⁰⁾ treated 1022 patients with HCV-cirrhosis and found that significantly fewer sustained responders developed HCC. Cox regression analysis showed that the risk of HCC development was not elevated in transient responders compared to the sustained responders but the risk is 7.9 times higher in non-responders than sustained responders. Benvegna *et al*⁽¹¹⁾ found that a smaller proportion of patients had worsening of their Child staging (7.9% vs 21.8%) and HCC development (5.6% vs 26.7%) after a median follow-up of 71.5 months.

The mean survival time of patients with HCC from the time of diagnosis to death is two to three months. The treatment of choice for patients with HCC is surgical resection, although curative surgery is only appropriate in 10-15% of cases. Chemotherapeutic agents such as **doxorubicin** offer a response rate of 20%. Transarterial chemoembolisation offers the cumulative survival rates of 51%, 13% and 6% at one, three and five years respectively⁽¹²⁾. In a randomised controlled trial by Lai *et al*⁽¹³⁾ on 71 patients with inoperable hepatocellular carcinoma treated with a high dose of **interferon**, a median survival of 14.5 weeks was achieved compared to 7.5 weeks in the placebo group. Objective tumour regression of more than 50% was observed in 31.4% and there was less tumour progression. Percutaneous ethanol injection was found to have an equivalent efficacy to surgery in the treatment of HCC in cirrhosis. Orthoptic liver transplantation is an alternative treatment for inoperable HCC but a recurrence rate of up to 65% and 5-year survival rates of 19.6-36% have been reported.

HEPATITIS C INFECTION AND LIVER TRANSPLANTATION

Hepatitis C re-infection following liver transplant is common, with no effective treatment or prophylaxis. The use of **interferon** for the treatment of HCV on the graft was disappointing due to the poor antiviral effect and the occurrence of chronic rejections in some patients. In a long-term follow-up of hepatitis C infection after liver transplantation by Gane *et al*⁽¹⁴⁾ the survival rates of 79%, 74% and 70% were reported at one, three and five years respectively. At a median follow-up of 35 months, 54% had evidence of mild chronic hepatitis and 27% moderate hepatitis. Eight percent had developed cirrhosis by 51

months. Graft loss was reported in 18% after a median survival of 303 days. The genotype 1b was associated with more severe graft injury. After five years, graft and overall survival are similar in patients with and without HCV. Methods to prevent and treat HCV re-infection on the graft are needed. Promising results of the combination therapy of **ribavirin** and **interferon** have been reported.

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