Treatment of children persistently infected with hepatitis B virus: seroconversion or suppression

Nicola Price and Elizabeth H. Boxall*

Health Protection Agency, West Midlands Public Health Laboratory, Heart of England NHS Foundation Trust, Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK

We have reviewed the current strategies regarding the treatment of persistent hepatitis B virus (HBV) in children and compared these with adult strategies. The options for achieving suppression of viral DNA replication versus hepatitis B e antigen to antibody seroconversion have been evaluated. The results of studies in different geographical locations have been confounded by HBV genotypes, as it is now clear that some genotypes respond better to treatment than others. Consideration needs to be given as to whether optimal treatment strategies developed for adults are directly applicable to children. In children, early seroconversion to allow improved long-term outcomes should be considered rather than embarking on the long-term complexities of managing patients on a combination of antiviral drugs to achieve viral suppression.

Keywords: HBV, antiviral therapy, DNA replication

Introduction

Hepatitis B virus (HBV) is a DNA virus that exists in a variety of genotypes with a distinct geographical distribution. There are eight designated genotypes, with A and D occurring in Africa, Europe and India, B and C in Asia, E in West Africa, F in Central and South America and G and H less well demarcated. In many parts of the world, the infection is transmitted perinatally or is acquired early in childhood. These early infections can become persistent, leading to chronic liver disease later in life; therefore, appropriate interventions to alter the natural history of this common infection are required. Until the impact of universal hepatitis B vaccination prevents hepatitis B infection in children, there will continue to be a need to treat those who have become infected.

The first antiviral agent with activity against HBV was alpha-interferon (IFN-α). A further development was pre-treatment with an immunosuppressive agent. Studies in adults established criteria associated with a favourable treatment response to IFN. These included hepatitis B e antigen (HBeAg) positivity, abnormal liver function tests (LFTs), evidence of inflammation by histology and a significant level of virus replication as judged by detectable HBV DNA. In addition, those who had acquired the infection in the last 5 years were more likely to respond to treatment than those who had been infected since birth. Ideally, therapy should induce a ‘seroconversion’ for HBeAg to anti-HBe antibodies (antiHBe) with a consequent reduction in HBV DNA levels, resolution of the liver histology and eventually a return to normality in transaminase enzymes. At best, with careful selection of patients, HBeAg to antiHBe seroconversion rates (at 5 years) of up to 56% (compared with 28% naturally clearing HBeAg) can be achieved, but with low rates of complete elimination of hepatitis B surface antigen (HBsAg) of 11.6% (0% naturally clearing). After extensive clinical trials in adults, these therapies were studied in children, who had been infected either perinatally or in the first few years of life through iatrogenic infection.

The HBV replication cycle has a step that requires DNA synthesis on an RNA template using a reverse transcriptase enzyme, a step in common with HIV. The antiretroviral drug lamivudine was shown to have activity against HBV in HIV-infected patients with dual infections. Originally exciting, within a few years, the issue of drug-resistant variants had arisen [substitutions in the tyrosine, methionine, aspartate, aspartate (YMDD) nucleotide-binding locus of the HBV polymerase], and these variants are now a management problem for those patients on therapy. Although different agents have become available and others are in development, the seroconversion rates at best have achieved 33%.

Intervention studies from different parts of the world will reflect the responses to treatment in the dominant genotypes within those locations, so it can be difficult to compare and evaluate studies. A number of studies have reported improved responses to IFN therapy in genotype A when compared with genotype D and in genotype B when compared with genotype C,
leading article

whereas nucleoside analogues have shown no relationship between response and genotype.1

Liver physicians have now moved to suppression of viral replication as a satisfactory endpoint with the anticipation that long-term suppression may lead to seroconversion or give a suitable outcome in terms of improvement in liver histology while the level of replication is kept low.

We now reconsider whether a ‘suppression strategy’ is appropriate for children, particularly for those who have been infected perinatally.

**Treatment options**

The American Association for the Study of Liver Diseases guidelines suggest that children with an elevated alanine transaminase (ALT) greater than two times normal should be considered for treatment with either IFN-α or lamivudine if the ALT levels remain elevated at the above level for longer than 6 months.10 However, a number of treatment strategies have been used in children, comprising IFN-α, IFN primed with prednisolone, lamivudine or a combination of IFN with lamivudine (summarized in Table 1).

**Interferon**

A treatment strategy of IFN-α 5 MU/m² three times weekly has been utilized with different durations of treatment (4–6 months) in HBeAg-positive children. A meta-analysis regarding its use in 240 children in Europe showed a significant difference in comparison with placebo regarding HBV DNA clearance [odds ratio (OR) 2.2] and HBeAg clearance, resulting in HBeAg clearance rates of 23% (10% placebo) after short-term follow-up.11 In addition, studies with long-term follow-up have shown HBeAg seroconversion and HBsAg clearance of 53.5% and 8.9% after 7 years of follow-up, respectively, in the treated group, versus 33.5% and 4% in those who naturally seroconverted.12 Although these results do not reach statistical significance, the cumulative rate of HBeAg seroconversion was statistically significant in treated children if the baseline ALT was twice the upper limit of normal (ULN) (64% versus 33%, \( P = 0.01 \)). Further long-term studies of mainly Caucasian patients (>5 years of follow-up) have shown that although the ultimate HBeAg clearance is similar between the treated and untreated groups (60%), the rate of HBeAg clearance is greater in treated when compared with untreated in the first 12 months, suggesting that IFN treatment accelerates a spontaneous event.13 The loss of HBsAg is also significantly greater between treated and untreated (25% versus 0%, \( P < 0.05 \)) in this study.13 However, in Chinese children14 and adults,15 IFN has been shown to have no effect. Thus genotype in children is likely to be an important factor in response to IFN. It has been shown in adults that infection with genotype B rather than genotype C,16 and with genotype A rather than genotype D17 gave an improved sustained response to IFN treatment.

The advantages of IFN therapy include a fixed treatment duration and no resistance, but the disadvantages include cost, need for injections and significant side effects (flu-like illness, myalgia, bone marrow suppression, weight loss and ALT elevation). Studies of pegylated IFN have not yet been published in children, although adult data are presented in a recent review.9 We would expect similar outcomes with respect to standard IFN therapy while achieving higher patient compliance.

**Interferon + prednisolone**

The rationale for steroid pre-treatment evolved from the clinical observation that patients often cleared HBV after tapering of steroid treatment, and it was reasoned that a transient transaminase flare-up was beneficial to clearance.18 A recent Cochrane meta-analysis19 comprising 13 studies and 790 patients has concluded that the loss of HBeAg and HBV DNA (OR 1.41 and 1.51, respectively) was significantly more frequent in those treated with sequential prednisolone and IFN-α than IFN-α alone. However, the effect on clinical outcomes (liver histology and life quality) could not be assessed. Six trials included only children, with a maximum follow-up of 2 years post-treatment, and the report concluded that there was no consistent trend in children with no significant results obtained (possibly due to insufficient sample size). However, a recent report20 has found the 5 year seroconversion percentages of prednisolone and IFN-α, IFN-α and placebo of 54%, 22% and 12%, respectively (\( P = 0.12 \)). In addition, evaluating the Asian (Indian subcontinent) subgroup, the OR was 5.9 [95% confidence interval (CI) 1.1–31.2] for untreated versus prednisolone plus IFN and 2.7 (95% CI 0.4–15.8) for untreated versus IFN alone. Thus, where possible, stored samples from clinical trials on therapeutic interventions could be genotyped and the outcome data re-evaluated.

**Lamivudine**

A sustained virological response has been reported after 3 years of follow-up for HBeAg seroconversion in 23% of children (13% placebo) after 1 year of therapy. The best response was achieved in those children with baseline ALT greater than twice ULN.21 Although an improved response of up to 29% has been attained after lamivudine therapy for 2 years, the rate of emergence of resistant variants carrying the YMDD motif increases with time (19% at 1 year, 49% at 2 years and 64% at 3 years) with a high dropout rate from therapy.22,23 The advantages of lamivudine therapy include oral administration, low cost and negligible side effects, but the disadvantages include virus resistance, cross-resistance to many new agents (entecavir, clevudine, telbivudine23,24 and from case reports adefovir25) and uncertainty regarding the optimal duration of therapy.

**Lamivudine and IFN**

Various strategies have been used, options being starting therapy simultaneously or sequentially (lamivudine then a combination) and ending with lamivudine alone in studies. The rationale is to reduce the viral DNA level to allow the IFN to work more effectively. Although sequential combination therapy was more beneficial than lamivudine or IFN monotherapy in adults,26 the complete response (HBeAg seroconversion, DNA suppression and normalization of ALT) in children in comparison with IFN monotherapy has not achieved statistical significance.27,28 Rates for complete response in simultaneous combination, sequential combination and IFN-only strategies were 49%, 34% and 33%, respectively.28 A number of papers have looked at different combination strategies but have not compared these with

1190
monotherapy or placebo, so true efficacy for such studies is difficult to interpret. In addition, these studies on combination therapy are too recent to assess long-term follow-up.

A recent paper has evaluated treatment in vertically infected children who are HBeAg-positive but with normal ALT and high DNA viral loads.29 These children would not normally be expected to respond to therapy. Treatment with lamivudine for 8 weeks then combined lamivudine and IFN-α for 10 months enabled 17% to establish complete virological control (HBsAg clearance), although 22% HBeAg seroconverted and 78% cleared DNA at the end of treatment. There was no YMDD resistance at 1 year. All four children who had cleared HBsAg had genotype B, Asian (China and Southeast Asia) and were female, and the other achieving HBeAg seroconversion had genotype D (European), indicating that genotype may play an important role.

Although combination therapy requires IFN injections and the associated IFN side effects, plus careful monitoring of viral resistance, the advantage of a finite period of therapy and a good level of success make this strategy worth further study.

Discussion

The goal of therapy for chronic HBV infection is to suppress or eliminate HBV DNA replication and so prevent progression to cirrhosis and hepatocellular carcinoma (HCC) or liver failure.

There are few clinical outcome data in children bar histological analysis in those treated with IFN.30 These data show no significant changes in fibrosis, but there was a significant difference in inflammatory response in the whole group, especially the responders at 12 months post-treatment. Thus, reasonable end-points in trials have been HBeAg seroconversion, HBsAg clearance, DNA clearance and ALT normalization, but very few include histology.

Seroconversion

The major advantage of early seroconversion is that further therapy is no longer necessary. This is more likely achieved with IFN with or without prednisolone to ‘kick-start’ a process that may first lead to HBeAg seroconversion and subsequently to HBsAg clearance. This has to be balanced against the disadvantages associated with the IFN therapy, the cost, route of administration and side effects.

Suppression

The use of lamivudine has shown a reduced likelihood of the development of HCC in adults.31 However, children are unlikely to continue long-term therapy because of the potential for the development of resistance. If combination antiviral treatments are adopted, the complexities of resistant variants would have to be managed accordingly. In addition, the effect of long-term antiviral therapy, particularly if started in childhood, is not known.

Genotypes

Hepatitis B genotype(s) has been shown to be important in the response in adults, an improved IFN response was shown in genotype B over genotype C16 and in genotype A over genotype D.17 In children, genotypes are also likely to have an important role, demonstrated by the poor response to IFN, with or without prednisolone priming in Chinese studies.14

Indicators for treatment

At present, children who are HBeAg-positive with ALT more than twice normal values for longer than 6 months are targeted for treatment.10 Children selected on that basis may start with either standard IFN-α or lamivudine therapy, whereas for adults, the preferred starting regimen would include pegylated IFN, adefovir or entecavir (lamivudine, telbivudine and standard IFN-α are also licensed for use).10 There is no mention of genotypes influencing the choice of treatment. An interesting paper29 on vertically infected children who were HBeAg-positive with normal ALT and high DNA viral loads showed 17% HBsAg clearance (complete virological control) when treated with both lamivudine and IFN-α. All four who cleared HBsAg were genotype B, Asian (China and Southeast Asia) and female. This paper challenges the view that perinatally infected immunotolerant children are unlikely to respond to antiviral therapy. In addition, genotype is clearly an important factor and published studies should be revised and updated to take this into account.

<table>
<thead>
<tr>
<th></th>
<th>IFN-α</th>
<th>IFN-α + glucocorticosteroids</th>
<th>Lamivudine</th>
<th>Lamivudine + IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg clearance</td>
<td>23% SD11</td>
<td>26% SD</td>
<td>55% NS</td>
<td></td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>53.5% (7 years)12 NS</td>
<td>54% NS</td>
<td>23% 37%</td>
<td></td>
</tr>
<tr>
<td>Suppression of HBV DNA</td>
<td>29% SD11</td>
<td>40% NS</td>
<td>61% 96%</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Resistance to antiviral agent</td>
<td>no</td>
<td>no</td>
<td>19% not evaluated</td>
<td></td>
</tr>
<tr>
<td>HBsAg clearance</td>
<td>8.9% (7 years)12 NS</td>
<td>0%</td>
<td>2% 18% NS</td>
<td></td>
</tr>
<tr>
<td>ALT normalization following treatment</td>
<td>39% SD11</td>
<td>58% NS</td>
<td>55% 85% SD</td>
<td></td>
</tr>
</tbody>
</table>

Reference(s) Torre et al.11 1996, Vo Thi Diem et al.12 2005 Boxall et al.20 2006 Jonas et al.21 2002 Dikici et al.27 2002

NS, not significant; SD, statistically different.
There is no consensus on the best age to start HBV treatment in children.

Outcome measures

Treatments should aim for improved long-term prognosis, normally represented either histologically or with a reduced progression to cirrhosis, liver failure and HCC. However, in the majority of studies surrogate end points such as improvement in LFTs, reduction in viral replication and HBeAg seroconversion are used. There are insufficient data on actual clinical outcomes and this must be addressed in the long-term.

Retaining therapeutic options for the future

Pegylated IFN, adefovir, entecavir, tenofovir, telbivudine and various combinations need to be considered for future trials and we look forward to reports of such combinations in adults.

Conclusions

There is a need for an effective strategy to achieve seroconversion in children to improve long-term outcomes without ‘closing off’ therapeutic options. Such a strategy is likely to evolve in the next few years as the results of combination therapies including interferon and antivirals are evaluated.

Transparency declarations

None to declare.

References