A 1-year trial of lamivudine for chronic hepatitis B in children
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Published in:
Journal of international medical research

DOI:
10.1177/147323000203000214

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2002

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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We carried out a 1-year trial to evaluate the efficacy and tolerability of lamivudine, an oral nucleoside analogue, in a small group of children with vertically acquired chronic hepatitis B. Patients were assessed for serum alanine aminotransferase (ALT) and serum hepatitis B virus (HBV) DNA at baseline and every 4 weeks thereafter, and for hepatitis B s antigen, hepatitis B e antigen and their antibodies every 12 weeks. Analysis of HBV mutation was undertaken at entry and on the occasion of the last positive control of HBV DNA. Lamivudine suppressed serum HBV DNA to undetectable levels in all treated patients within 24 weeks. Serum ALT levels returned to normal values within 36 weeks. Therapy was well tolerated, and although nausea and vomiting were reported in one child, it was not necessary to stop treatment. A new observation was that, contrary to previous data, seroconversion appeared to occur earlier in children with lower ALT levels at baseline.

**KEY WORDS:** LAMIVUDINE; NUCLEOSIDE ANALOGUE; CHRONIC HEPATITIS B; CHILDREN; VERTICAL TRANSMISSION

### Introduction

Interferon alpha (IFN) is the only treatment specifically approved for chronic hepatitis B in children.\(^1\) Administered by injection, IFN has potentially dose-limiting side-effects and its efficacy is variable.\(^2\) Lamivudine, an oral nucleoside analogue, has shown to reduce hepatitis B virus (HBV) levels and to suppress progressive liver damage in adults.\(^3\) Specific mutations, e.g. substitution of either valine or isoleucine for the amino-acid position 552 methionine in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV polymerase gene (domain C of reverse transcriptase) appears to confer resistance to lamivudine. Other mutations of lamivudine-resistant HBV reverse transcriptase occur in the B domain: one is a leucine to methionine change at position 528 and occurs in parallel with the methionine to valine change at position 552.\(^4\)

### Patients and methods

We carried out a 1-year trial to evaluate the efficacy and tolerability of lamivudine in children with chronic hepatitis B. From December 1999, 10 children with vertically acquired chronic hepatitis B were followed from birth in the Infectious Disease Unit of the Paediatric Department, San Paolo Hospital, and evaluated for a longitudinal study.

To be eligible, children had to be at least 6 years of age, to have a chronic infection
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defined as serum hepatitis B s antigen (HBsAg) and hepatitis B e antigen (HBeAg) positive, serum alanine aminotransferase (ALT) levels at least 1.3 times the upper limit of the normal range and detectable levels of serum HBV DNA. Patients with previous treatment for hepatitis B or patients with hepatitis C and D viruses or human immunodeficiency co-infection were excluded. Children received oral lamivudine 3 mg/kg (maximum 100 mg) per day. The patients were assessed at clinic visits for serum ALT and serum HBV DNA (hybridization assay) every 4 weeks and for HBsAg, HBeAg and their antibodies every 12 weeks. Analysis of HBV mutation was undertaken at entry and on the occasion of last positive control of HBV DNA. The DNA sequence of the polymerase gene was determined directly from polymerase chain reaction products. The region from amino acid 459 to amino acid 558, which includes domains B (aa 511 – 537) and C (aa 548 – 558) of the viral reverse transcriptase, was studied.

At each clinic visit, data concerning adverse effects were collected. The study was approved by the Centre’s Ethics Committee and all parents gave written consent before enrolment.

Results

Four of 10 children, three females and one male, median age 9.0 years (SD ± 2.3) were eligible. Table 1 shows the basal characteristics of the patients, the serum ALT and HBV DNA levels (median ± SD) observed in the 12 months before treatment.

Lamivudine suppressed serum HBV DNA to undetectable levels in all treated patients within 24 weeks (in case 1 at 4 weeks, case 4 at 8 weeks and cases 2 and 3 at 24 weeks) and levels remained undetectable throughout the follow-up period. Serum ALT levels returned to normal values in cases 1 and 4 within 12 weeks and in the other two cases within 36 weeks, and remained so during follow-up. HBeAg seroconversion, defined as the loss of detectable levels of HBeAg and the appearance of antibody to HBeAg, was observed in cases 1 and 4 at 12 weeks, case 3 at 24 weeks and case 2 at 36 weeks. Earlier seroconversion was obtained in children with lower median ALT levels at baseline. None cleared HBsAg. No amino-acid mutations were detected in the YMDD motif in serum samples collected from the four children before lamivudine treatment or in the two children still HBV DNA positive after 6 months of therapy.

Lamivudine was well tolerated. Nausea and vomiting were reported in one child only during the first week of treatment, but they were not sufficiently severe to warrant stopping treatment.

Discussion

The rate of HBeAg seroconversion reported in different studies carried out in adult patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex (m/f)</th>
<th>Age (years)</th>
<th>Serum ALT (U/ml) median ± SD</th>
<th>Serum HBV DNA (pg/ml) median ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>6.2</td>
<td>88 ± 17</td>
<td>251 ± 880</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>8.1</td>
<td>180 ± 66</td>
<td>819 ± 781</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>9.8</td>
<td>208 ± 63</td>
<td>1885 ± 311</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>11.8</td>
<td>75 ± 13</td>
<td>582 ± 175</td>
</tr>
</tbody>
</table>
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treated with lamivudine ranges from 16% to 35%.\textsuperscript{3,5} Data concerning lamivudine treatment in children are few, and the results of long-term therapy are not known. In a recent study, Kocak \textit{et al.}\textsuperscript{6} reported a low clearance (7.4%) and seroconversion to anti-HBe (5.6%) in chronic hepatitis B children treated with lamivudine for 52 weeks. In our study we observed viral clearance and HBeAg seroconversion in all children within 12 months of treatment. A correlation has been observed between lower serum ALT levels at baseline and timing of seroconversion, contradictory to the previous data in which a high baseline ALT level was a predictive parameter for response.

In conclusion, our preliminary results seem to confirm the efficacy of lamivudine in the treatment of chronic hepatitis B in children. An earlier seroconversion in children with lower ALT levels at baseline is a new observation. If this interesting result is confirmed in larger studies, predictive parameters for response to lamivudine therapy could be reconsidered.

\begin{itemize}
  \item Received for publication 25 October 2001 • Accepted 31 October 2001
\end{itemize}

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