Recombinant human interferon alfa-2b treatment for acute non-A, non-B hepatitis

N C Tassopoulos, M G Koutelou, G Papatheodoridis, H Polychronaki, I Delladetsima, T Giannikakis, A Todoulos, A Toliopoulos, A Hatzakis

Abstract
To assess the safety and possible efficacy of recombinant human interferon alfa-2b in preventing the development of chronic hepatitis, 24 adults (eight men, 16 women) with acute non-A, non-B (NANB) hepatitis were recruited to a pilot study. Half of the cases were parenterally transmitted and half were community acquired. Twelve patients received 3 million units (MU) interferon three times weekly subcutaneously for six weeks and the remaining 12 patients received no treatment. Anti-hepatitis C virus (HCV) was detected in 14 (58.3%) of the 24 patients. The alanine aminotransferase activity returned to normal in nine of 12 interferon alfa-2b treated patients and six of 12 controls by week 52. Interferon alfa-2b was well tolerated, even in jaundiced patients, who only complained of mild flu like syndrome during the first week of treatment. These data are consistent with the hypothesis that interferon alfa-2b may help prevent progression to chronic hepatitis (interferon alfa-2b 25%v controls 50%), particularly in anti-HCV negative cases (interferon alfa-2b none of six v controls two of four). A randomised, double blind placebo-controlled trial is required, however, to substantiate these results further.

Methods
Twenty four Greek adults (eight men, 16 women) with acute NAB hepatitis took part. They were divided into two groups: group I consisting of 12 patients who received 3 million units (MU) of interferon alfa-2b (INTRON A, Schering Plough, Kenilworth, NJ) three times a week subcutaneously for six weeks and group II comprising 12 patients matched to group I for sex, age, and risk factors, but who received no treatment. The demographic features of these patients are shown in Table I. Blood samples were obtained weekly for the first month after treatment, twice weekly for the second month, every month for the next four months, and then every two months for the next six months.

The criteria for diagnosis of acute viral hepatitis were: symptoms and signs of hepatitis of less than one month's duration; peak serum alanine aminotransferase (ALT) activity equal to or greater than eight times the upper limit of normal (46 IU/l); and exclusion of other possible causes of liver injury (for example pre-existing liver disease, alcohol abuse, drugs, autoimmune hepatitis). Acute NANB hepatitis was defined by the absence of serological markers for acute hepatitis A (IgM anti-hepatitis A virus (HAV) negative), acute hepatitis B (hepatitis B surface antigen (HBsAg) negative and/or IgM anti-hepatitis B core (HBc) negative), and acute Epstein-Barr virus infection (IgM antibody to Epstein-Barr virus capsid antigen negative). Progression to chronic hepatitis was characterised by raised ALT activity one year after the onset of the acute episode. Commercially available enzyme immunoassays (Abbott Labs, North Chicago, IL) were used for the detection of HBsAg, IgM anti-HBc, and IgM anti-HAV. IgM antibody to the viral capsid antigen of Epstein-Barr virus was determined by indirect immunofluorescence. Ninety six serum specimens were tested for antibodies to hepatitis C virus (HCV) by Abbott's second generation enzyme immunoassay. This assay is based on recombinant HCV non-structural antigens derived from the NS4 (c100) and NS3 (33c) regions, and on a structural antigen derived from the S' region of the HCV genome (putative core). One or two repeatedly reactive samples per patient were confirmed by a second generation recombinant immunoblot.
TABLE 1 Demographic, biochemical, and serological features of 24 patients with acute non-A, non-B hepatitis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Interferon alfa-2b</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No studied</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Men/women</td>
<td>4/8</td>
<td>4/8</td>
</tr>
<tr>
<td>Age (SD) (y)</td>
<td>46.2 (0.9)</td>
<td>50.2 (1.5)</td>
</tr>
<tr>
<td>Transfusions</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Needlestick injury</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>None (sporadic)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Peak alanine aminotransferase (IU/l) (mean (SD))</td>
<td>1120-1 (333-6)</td>
<td>1008-7 (524-8)</td>
</tr>
<tr>
<td>(range)</td>
<td>(710-1808)</td>
<td>(467-2078)</td>
</tr>
<tr>
<td>Peak bilirubin (mg/dl) (mean (SD))</td>
<td>12.3 (13.5)</td>
<td>10.8 (6.0)</td>
</tr>
<tr>
<td>(range)</td>
<td>(0.9-51.6)</td>
<td>(0.9-18.9)</td>
</tr>
<tr>
<td>Anti-HCV positive</td>
<td>6 (50%)</td>
<td>8 (67%)</td>
</tr>
</tbody>
</table>

*Occurring within six months before the onset of hepatitis.

Results

The biochemical profile (peak ALT, peak bilirubin) before treatment was similar in the two groups of patients studied (Table 1). Acute hepatitis was icteric (bilirubin >34 μmol/l) in 11 (92%) patients randomised to interferon treatment and 11 (92%) control patients. Anti-HCV was detected in six (50%) interferon alfa-2b-treated and eight (67%) untreated patients. Anti-HCV appeared early (three to 30 days after the onset of hepatitis) in the serum of four treated and eight untreated subjects; two treated patients became seropositive for anti-HCV, 41 and 51 days respectively after the onset of hepatitis.

Histological lesions were classified as moderate in two and severe in four of the six interferon alfa-2b-treated community acquired cases of hepatitis. In contrast, lesions were classified as mild in one, moderate in three, and severe in one of the five untreated community acquired cases with a biopsy specimen available at the acute phase. Possible transition to chronic hepatitis and/or cirrhosis was observed in three of six interferon alfa-2b-treated and two of five control cases.

The ALT returned to normal in nine of 12 interferon alfa-2b-treated and three of 12 control patients at the end of treatment (week six). During follow up (week eight to week 52), the ALT returned to normal in three treated patients and three of the untreated patients who had abnormal enzyme activities at the end of week six. In contrast, three treated patients who had normal ALT values at the end of week six relapsed and developed chronic hepatitis; these patients were seropositive for anti-HCV. ALT changes in three treated and three control patients are shown in Figures 1 and 2, respectively. Anti-HCV remained detectable in all except one treated patient, who became seronegative seven months after anti-HCV seroconversion; this patient had self-limited hepatitis, and was the only case of anti-HCV seroreversion out of 117 anti-HCV positive patients included in the follow up study (Tassopoulos et al, unpublished data).

Figure 1 Three adult patients with acute non-A, non-B hepatitis treated with 3 MU of interferon alfa-2b three times weekly for six weeks. Two patients had normal alanine aminotransferase (ALT) activities at the end of treatment (week six). One of these relapsed after stopping treatment and developed chronic hepatitis. The third patient had raised ALT values at the end of week six. The ALT had returned to normal by week eight, however, and remained normal during follow up.

Progression of acute NANB hepatitis to chronic hepatitis was observed less frequently in treated anti-HCV negative patients (none of six v two of four), men (one of four v four of four), and in sporadic cases (none of six v three of six) (Table II).

Interferon alfa-2b was well tolerated, even in jaundiced patients, who complained only of mild flu like syndrome during the first week of treatment. Neither leukopenia nor thrombocytopenia were observed, and none of the patients showed biochemical exacerbation or clinical deterioration of acute hepatitis during the six week treatment period.

Discussion

The study showed that interferon alfa-2b is safe and well tolerated, even in jaundiced patients with acute NANB/C hepatitis, and reconfirmed our previous findings in acute


Recombinant human interferon alfa-2b treatment for acute non-A, non-B hepatitis.

N C Tassopoulos, M G Koutelou, G Papatheodoridis, H Polychronaki, I Delladetsima, T Giannikakis, A Todoulos, A Toliopoulos and A Hatzakis

Gut 1993 34: S130-S132
doi: 10.1136/gut.34.2_Suppl.S130

Updated information and services can be found at:
http://gut.bmj.com/content/34/2_Suppl/S130

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/