Interferon-α and Ribavirin in Treating Children and Young Adults With Chronic Hepatitis C After Malignancy

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ABSTRACT. Objective. Chronic hepatitis C is a major long-term problem for children who survive cancer. Interferon (IFN)-α has been shown to be effective in treating patients with chronic hepatitis C; however, the rate of sustained response is low. Combining IFN-α and ribavirin (RBV) has been shown to significantly improve the response in adult patients with chronic hepatitis C. The aim of this pilot study was to evaluate the efficacy and safety of a combined virostatic treatment with IFN-α and RBV in a small cohort of children and adolescents with chronic hepatitis C and previous malignancy.

Methods. Twelve patients with a history of a hematologic disease (median follow-up: 13.5 years; range: 7–14.7 years) and chronic hepatitis C were treated with recombinant IFN-α-2a (6 megaunits/m² body surface area, 3 times a week, subcutaneously) combined with RBV (15 mg/kg body weight/day, orally) for 12 months. They were tested monthly for blood counts and liver function, and for serum virus concentrations (hepatitis C virus RNA by polymerase chain reaction) every 3 months.

Results. At the end of the treatment, hepatitis C virus RNA could not be detected in the serum of 8 of the 12 patients; 2 of these patients relapsed soon after therapy withdrawal, whereas 6 patients maintained in sustained virologic and biochemical remission (follow-up: 12 months). Treatment-induced toxicity was moderate and reversible with influenza-like symptoms and a decrease in blood counts in all 12 patients, alopecia in 5 of the 12, hemolysis in 4 of the 12, and weight loss of >10% in 2 of the 12.


ABBREVIATIONS. HCV, hepatitis C virus; IFN, interferon; RBV, ribavirin; PCR, polymerase chain reaction; ALT, alanine aminotransferase; IC, internal control.

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Received for publication Jan 21, 2000; accepted Apr 25, 2000.

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PEDIATRICS (ISSN 0031-4005). Copyright © 2000 by the American Academy of Pediatrics.
combination therapy with IFN and RBV in children with chronic HCV infection.

The aim of the present pilot study was to evaluate the safety and efficacy of IFN/RBV therapy for children, adolescents, and young adults with chronic hepatitis C after a previous malignancy.

METHODS

Patients

Twelve children or young adults (7 males and 5 females) who were cured of a malignant pediatric hematologic-oncologic disease (median follow-up: 13.5 years; range: 8–15.7 years) entered the present study. Median age at diagnosis of the underlying disease was 4.6 years (range: 1.1–14.7 years), median age at study entry was 17.1 years (range: 10.6–31 years). All patients had chronic HCV infection defined by detectable circulating HCV RNA for >6 months. None had signs of concomitant infection with human immunodeficiency virus, hepatitis B virus, cytomegalovirus, or Epstein-Barr virus. Other causes of liver damage (such as α1-antitrypsin deficiency, Wilson’s disease, and autoimmune hepatitis) were also excluded. Liver biopsies were performed percutaneously by the Menghini technique before study entry but were not performed at completion of therapy. Determination of fibrosis score and hepatitis activity index was performed according to the criteria and recommendations by Chevallier et al27 and Bianchi et al,28 respectively. The HCV subtype was determined by genotyping and serotyping in 11 of 12 patients. All patients had HCV subtype 1, including genotype 1a in 4 patients, genotype 1b in 6 patients, and mixed genotype 1a/1b in 1 patient. None of the patients had received IFN before entering the study. Treatment results were updated on March 31, 2000.

Treatment Protocol

The patients received recombinant IFN-α-2a (Roferon, Hoffmann-La Roche SA, Basel, Switzerland) at a dose of 6 megaunits/m² body surface area, subcutaneously 3 times a week, combined with RBV (Distri Drug, Morschwiller Le Bas, France) at a dose of 15 mg/kg body weight/day orally. The duration of treatment was 12 months. Clinical evaluation, complete blood count, and liver function tests were performed before, monthly during therapy, and then every 3 months during follow-up. The presence of serum HCV RNA by polymerase chain reaction (PCR) was tested before IFN/RBV therapy, 1 month after the start of therapy, and then every 3 months during follow-up. The serum HCV RNA profiles during therapy and follow-up are shown in Table 1. Determination of fibrosis score and hepatitis activity index was performed according to the criteria and recommendations by Chevallier et al and Bianchi et al., respectively. The HCV subtype was determined by genotyping and serotyping in 11 of 12 patients. All patients had HCV subtype 1, including genotype 1a in 4 patients, genotype 1b in 6 patients, and mixed genotype 1a/1b in 1 patient. None of the patients had received IFN before entering the study. Treatment results were updated on March 31, 2000.

Liver Function and Virologic Testing

The serum alanine aminotransferase (ALT) values were determined by a standard autoanalyzer. The upper limit of normal ALT was 23 IU/L. For quantitation of serum HCV RNA, the Cobas Amplicor HCV Monitor Test (Roche Diagnostic Systems, Pleasanton, CA) was used. QuantiTect PCR was performed using the Cobas Amplicor HCV Test (Roche Diagnostic Systems). For genotyping, the Inno-LiPA HCV II assay (Innogenetics NV, Zwijndrecht, Belgium) was used.

RESULTS

Response to Treatment

At study entry all patients had histologic features of active hepatitis with mild disease activity, the ALT values were abnormal in 5/12 patients (median: 22; range: 9–70 IU/L). At the end of treatment, ALT values were normal in all patients (median: 10; range: 5–20 IU/L). HCV RNA was detected in the baseline sera of all patients with a median level of 2.0 × 10⁵ copies/mL (range: 2.2–5.6 × 10⁵ copies/mL). Table 1 shows the serum HCV RNA profiles before, during, and after IFN/RBV treatment. Three months after the start of treatment serum HCV RNA was no longer detectable in 9/12 patients (75%), while 3 patients never cleared HCV RNA. One patient (patient 12) cleared HCV RNA from serum within 3 months, but HCV RNA reappeared during treatment. At the end of IFN/RBV treatment 8/12 patients were HCV RNA-negative: 2 relapsed soon after therapy withdrawal, whereas 6 remained negative for at least 12 months after cessation of therapy. Sustained response was, therefore, obtained in 6/12 patients (50%).

Complications

IFN/RBV treatment was well tolerated and all side effects were transient and reversible. All patients exhibited a mild influenza-like syndrome during the

<p>| TABLE 1. Serum HCV RNA Profiles During Therapy and Follow-Up |
| --- | --- | --- | --- | --- | --- | --- |</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Years)</th>
<th>Gender</th>
<th>HCV Subtype</th>
<th>Histology</th>
<th>IFN/RBV Therapy (Months)</th>
<th>Follow-Up (Months)</th>
<th>Response</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>21</td>
<td>Male</td>
<td>1b</td>
<td>MH</td>
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<td>1 6 9 12</td>
<td>1 6 9 12</td>
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<tr>
<td>2</td>
<td>14</td>
<td>Female</td>
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</tr>
<tr>
<td>3</td>
<td>31</td>
<td>Female</td>
<td>1a</td>
<td>CH-MOA</td>
<td>2</td>
<td>0 1 6 9 12</td>
<td>1 6 9 12</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>Male</td>
<td>1b</td>
<td>CH-MA</td>
<td>1</td>
<td>0 1 6 9 12</td>
<td>1 6 9 12</td>
</tr>
<tr>
<td>5</td>
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<td>Male</td>
<td>1a</td>
<td>MH</td>
<td>0</td>
<td>0 1 6 9 12</td>
<td>1 6 9 12</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>Female</td>
<td>1a</td>
<td>MH</td>
<td>11</td>
<td>0 1 6 9 12</td>
<td>1 6 9 12</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
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<td>1b</td>
<td>CH-MA</td>
<td>1b</td>
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<td>1 6 9 12</td>
</tr>
<tr>
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<td>28</td>
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<td>CH-MA</td>
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<td>0 1 6 9 12</td>
<td>1 6 9 12</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
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<td>1 6 9 12</td>
</tr>
<tr>
<td>10</td>
<td>21</td>
<td>Female</td>
<td>1a, 1b</td>
<td>CH-MA</td>
<td>1</td>
<td>0 1 6 9 12</td>
<td>1 6 9 12</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
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<td>1b</td>
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<td>1 6 9 12</td>
</tr>
<tr>
<td>12</td>
<td>17</td>
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<td>1a</td>
<td>CH-MA</td>
<td>1</td>
<td>0 1 6 9 12</td>
<td>1 6 9 12</td>
</tr>
</tbody>
</table>

● indicates HCV RNA (+); ○, HCV RNA (−); HAI, hepatitis activity index; FS, fibrosis score; CH-MOA, chronic hepatitis with moderate activity; CH-MA, chronic hepatitis with mild activity; MH, minimal hepatitis; ND, not done.
first weeks of treatment. There were decreases in leukocyte and platelet counts and hemoglobin levels after the beginning of IFN/RBV therapy in all patients. However, none of the patients showed a leukocyte count below 1.500/μL, a platelet count below 100 × 10^3/μL, or a hemoglobin below 11 g/dL. Five patients complained about transient hair loss, which required a 10% reduction of IFN in 3 of them. Additional side effects were mild hemolysis in 4/12 patients and a >10% loss of body weight in 2 patients. Neurological or psychological side effects, aseptic bone necrosis, or reactions at injection sites were not observed in our patients.

**DISCUSSION**

Little information is available about the efficacy of IFN in the treatment of children or adolescents with chronic hepatitis C. There are only a few pilot studies with small patient numbers, heterogeneous viral HCV populations, and different treatment protocols.15–23 The achieved sustained response rates ranged between 0% and 56% of the patients.15–23 However, Pensati et al23 recently observed a low virological response of only 8% in 25 children treated with IFN monotherapy for chronic hepatitis C. The most important factors in predicting IFN response seem to be HCV genotype, pretreatment HCV RNA titers, an underlying hematopoietic disease, and absence of cirrhosis.14,16,17,19 In view of these results, and because controlled trials with sufficient numbers of patients are lacking, many pediatricians are reluctant to use IFN as monotherapy for chronic hepatitis C in children.

RBV inhibits the replication of many different viruses including HCV.24 Pilot studies of adult patients suggested that combining IFN with RBV is more effective than using IFN alone.13,24,25 McHutchison et al26 randomly assigned 912 adult patients with chronic hepatitis C to receive standard dose IFN alone or in combination with RBV (1000 or 1200 mg orally per day) for either 24 weeks or 48 weeks, respectively. The rate of sustained response was higher among patients who received combination therapy for 24 weeks (31%) or 48 weeks (38%), compared with patients receiving IFN monotherapy for 24 weeks (6%) or 48 weeks (13%). Combination treatment was generally well tolerated, and the observed side effects (including nausea, fatigue, hemolysis, pancytopenia, anorexia, and emotional lability) were acceptable and reversible.13,25,26 Because there were no data in the literature on IFN/RBV therapy in children with chronic hepatitis C, a similar regimen as in adults was used in the present study.

The results of the present pilot study suggest that, as in adult patients, the combination therapy with IFN and RBV may also be beneficial in children and adolescents with chronic HCV infection. In fact, 50% of the patients achieved a sustained response with HCV RNA negativity for >12 months after completion of therapy. This response rate is of note because all patients were survivors of previous malignant hematopoietic diseases and all patients had HCV genotype 1, factors usually predicting a poor response to IFN treatment. It was interesting to observe that of the 6 sustained responders, 4 had cleared HCV from serum by month 1 and 2 by month 3. The observed adverse effects were mild and reversible in all patients; only 3 of 12 patients required a 10% dose reduction of IFN.

**CONCLUSION**

The results of this small pilot study are encouraging and prompt further investigation. However, 50% of the patients did not respond to combination therapy with IFN and RBV. Whether these patients will respond to higher doses or longer courses of treatment or new antiviral drug combinations needs to be investigated.

**REFERENCES**

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Pediatrics 2000;106:e53

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*Pediatrics* 2000;106;e53

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