Introduction

The therapeutic strategy for chronic hepatitis C has changed dramatically since consensus interferon (rIFN-αcon1, Advaferon) and the ribavirin (Rebetol) + IFN-α-2b (Intron A) combination therapy were approved in December 2001 and the limitations to the administration period of existing IFN-α preparations were abolished in February 2002.

This paper describes the indications and future issues for rIFN-αcon1 based on clinical study results.

Outline of rIFN-αcon1 (consensus interferon)

This preparation has 166 amino acid residues and a molecular weight of 19,500 Daltons. The number of amino acid residues is almost the same as that of existing IFN-α preparations. Thirteen subtypes of IFN-α with different activities were known in 1982. A new amino acid sequence was designed according to the hypothesis that a useful IFN preparation could be created by choosing a frequent amino acid at each site of amino acid sequences (consensus-sequence theory; Fig. 1). rIFN-αcon1 was produced with synthetic DNA based on the amino acid sequence. It was then purified and extensively analyzed for its properties before it was introduced into clinical studies.
acid sequence in a gene-recombinant *Escherichia coli* expression strain. Since this preparation had a high affinity for Type 1 IFN receptors and was superior to a control IFN preparation in antiviral effect, cell growth-inhibiting effect, and immuno-stimulating effect, clinical studies were started in 1991 in USA and in 1993 in Japan.

Unlike existing IFN-α preparations, it is supplied as a subcutaneous injection at a small volume (0.4 ml for 12 MIU and 0.6 ml for 18 MIU) without human serum-derived albumin.

**Clinical Results of rIFN-αcon1**

Although rIFN-αcon1 has been clinically applied, no major results have been published yet. Therefore, the results of a randomized controlled study using the IFN-αcon1 preparation as a control are described here. rIFN-αcon1 was subcutaneously administered at 18 or 12 MIU/day for 2 weeks consecutively, followed by thrice weekly for 22 weeks to determine the rate of patients with virologic complete response (CR) (defined as negative for amplicor determination) and normal ALT at the time after 24 weeks from the end of treatment.

1. **Group with high viral load**
   
   (≥100 kcopies/ml or ≥1 Meq/ml)

   rIFN-αcon1 produced a CR rate of 26.3%
CONSENSUS INTERFERON FOR CHRONIC HEPATITIS C

(25/95) (Fig. 2) and a normal ALT rate of 43.8% (35/80) in the 18 MIU treated group. It produced a CR rate of 16.7% (11/60) and normal ALT rate of 35.1% (20/57) in the patients with hepatitis of genotype 1b, who are considered particularly intractable among those with high blood viral load. The CR rate was significantly higher than that of the control group (p<0.05). The CR rate was also higher than that of existing IFN-α preparations (0 to 8.6%). Figure 3 shows the CR rate by pretreatment viral load in patients with hepatitis of genotype 1b and high viral load. Although the CR rate tended to fall as the viral load was increased, a high CR rate of 27.5% (11/40) was obtained for the group with a viral load from 100 to less than 700 kcopies/ml. In contrast, rIFN-α-con1 produced a CR rate of 0% in patients with hepatitis of 1b genotype and a high viral load of 300 kcopies/ml or higher.

2. Group with low viral load
(<100 kcopies/ml or <1 Meq/ml)

rIFN-α-con1 at 12 MIU produced a CR rate of 73.3% (22/30), with no difference among genotypes (Table 1). It was more effective than existing IFN-α preparations (49.1 to 66.0%) in the patients with low viral load as well.

3. IFN re-treatment group

rIFN-α-con1 was administered at 18 MIU in patients in whom previous IFN therapy made HCV RNA negative or ALT return to normal, but did not achieve CR. The results showed it achieved CR in 40.0% (14/35) and made ALT persistently normal in 77.8% (7/9) (Table 2). This indicates that the preparation is clinically significant for those re-treated with IFN as much as for those treated for the first time. In addition, rIFN-α-con1 produced a CR rate of 0% in patients with hepatitis of 1b genotype and a high viral load of 300 kcopies/ml or higher.

4. Safety

All the 227 patients treated with rIFN-α-con1 experienced at least one adverse reaction: fever developed in 98.2%, general malaise in 45.4%, anorexia in 39.6%, headaches in 39.2%, arthralgia in 32.6%, insomnia in 27.8%, alopecia in 27.8%, and gastric discomfort in 20.3%. Although all these adverse reactions

<table>
<thead>
<tr>
<th>Pretreatment viral load (kcopies/ml)</th>
<th>Genotype</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1b</td>
<td>2a</td>
</tr>
<tr>
<td>≥100</td>
<td>12.5% (2/16)</td>
<td>100% (9/9)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>6.7% (1/15)</td>
<td>100% (3/3)</td>
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Table 1: HCV RNA-Negative Rate by Genotypes in Patients with Low Viral Load

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Total</th>
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<tbody>
<tr>
<td>1b</td>
<td>71.4% (10/14)</td>
</tr>
<tr>
<td>2a</td>
<td>75.0% (12/16)</td>
</tr>
<tr>
<td>2b</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>73.3% (22/30)</td>
</tr>
</tbody>
</table>

Table 2: HCV RNA-Negative Rate by Viral Loads and Genotypes in Patients Treated with IFN for the Second Time

( ): number of cases
were already known, it should be noted that they tended to develop at higher incidences than with previous IFN-α preparations. Depression, a serious adverse reaction to IFN, was observed in 5% or higher. Sho-saiko-to is contraindicated in patients treated with rIFN-αcon1. Further, it is recommended that the combination of rIFN-αcon1 with theophylline, antipyrine, or warfarin be performed with care because the IFN preparation inhibits the activities of enzymes responsible for drug metabolism in the liver.

**Indications and Future Issues of rIFN-αcon1**

Considering the above clinical results, this preparation is indicated for patients with 1b genotype and a high viral load of up to 700 KIU/ml, in addition, it is expected to show higher efficacy than existing IFN-α preparations in the groups with 2a genotype and high viral load, or with low viral load. Although the ribavirin + IFN-α2b combination therapy is also indicated for patients with a high viral load, it has a drawback in that ribavirin causes hemolytic anemia. Therefore, rIFN-αcon1 is recommended as the first line treatment for the patients with blood Hb around 12 g/dl or lower. Since the clinical study of this preparation was performed in a relatively small number (less than 300) of patients, it goes without saying that verifying the efficacy and safety of rIFN-αcon1 is required.

To further improve the therapeutic results of rIFN-αcon1 in patients in the intractable 1b/ high viral load group, it would be valuable to create a polyethylene glycol (PEG) preparation of rIFN-αcon1 or combine rIFN-αcon1 with ribavirin.

**REFERENCES**

4) Walter, M.R.: Three-dimensional models of interferon-α subtypes IFN-con1, IFN-α8, and IFN-α1 derived from the crystal structure of IFN-α2b. *Semin Oncol* 1997; 24(S9): 52–62.