Moreover, about 20-30% of patients suffering from HCV correlated chronic hepatitis will develop hepatic cirrhosis within about 20 years and about 3% are likely to suffer from hepatocarcinoma within the following 10 years. HCV virus comprises different genotypes, at least 8 of them, which are divided into subtypes. The nomenclature made by Simmonds et al. is by now currently used to classify the different HCV genotypes.

Different geographical areas highlight a different prevalence of the various genotypes. In Italy the most frequent ones are:

a) HCV1 (especially subtype 1b);

b) HCV2 (in particular the subtype 2c);

c) HCV3.

At present the only therapy whose therapeutic efficacy has been demonstrated for the treatment of chronic hepatitis C is represented by interferon.

Although there are three types of interferon, α, β, γ, only the first two types are used in clinical practice.

Clinical studies available at the moment do not seem to provide precise information about the real efficacy of interferon therapy in patients above 65. This interpretation is essentially based on the slow evolution of viral chronic hepatitis. However, it is also true that patients with clinical and histological evidence of a disease with rapid evolution can be treated with IFN if their life expectancy is sufficiently long (> 5 years). It is in accordance with these data and following this consideration that our studies on elderly patients have been conducted.

In the light of the above mentioned controversies about the use of interferon in the treatment of chronic hepatitis C in the elderly, which is a much debated question, we aim to
analyse three of our previous studies relative to therapy with different types of interferon in elderly patients suffering from HCV correlated chronic hepatitis. Our aim is to ascertain the best interferon therapy as well as the one which is particularly effective in the elderly and with less side-effects as possible\textsuperscript{12-14}.

We take into examination three different studies conducted by our-selves in the latest years.

I) The first study\textsuperscript{12} was performed on 20 patients with an age ranging between 60 and 69 years (14 women and 6 men) suffering from HCV correlated chronic hepatitis (Table I). In this study the patients were subjected to therapy with recombinant interferon alpha 2b, and they were given a 3 MU dose via IM, in alternate evenings for a period of six months.

II) The second work\textsuperscript{13} deals with a comparative study conducted on 26 patients with an age ranging between 60 and 75 years (average age 65) alternatively assigned to a group consisting of patients treated with \( \beta \)-interferon or to another control group of patients who were treated with non-specific therapy (Table II). The patients belonging to the I group were treated with a 3MU dose via IM of \( \beta \)-IFN given in alternate evenings for two months and later on for other 10 months 6MU via IM of \( \beta \)-IFN were given in alternate evenings.

III) The third study\textsuperscript{14} was performed on a sample of 100 patients with an age ranging between 60 and 74 years (Table III) suffering from HCV correlated chronic hepatitis and with a life expectancy above 10 years. The patients were subdivided at random into two groups of 50 patients each: the first group was given a 3MU dose via IM of lymphoblastoid IFN in alternate evenings for two months and then 6MU via IM in alternate evenings for another 10 months. The second group was given non-specific therapy (fructose 1-6 diphosphate/glucose/B vitamins/A coenzyme) for 12 months.

Evaluation of histological data in the studies was done by using Knodell index\textsuperscript{15}. Histological evaluation using such index, which evaluates the lobular inflammation, intralobular degeneration and local necrosis, portal inflammation and fibrosis, was performed before and at the end of each single treatment.

### Table I. Patients treated with recombinant interferon alpha.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Histology</th>
<th>Contagion</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 females</td>
<td>60-69</td>
<td>cae = 11 cases</td>
<td>transfusion = 11 cases</td>
</tr>
<tr>
<td>14 males</td>
<td></td>
<td>pce = 7 cases</td>
<td>unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n.b. = 2 cases</td>
<td>= 9 cases</td>
</tr>
</tbody>
</table>

cae = chronic active hepatitis; pce = persistent chronic hepatitis; n.b. = no-biopsy.

### Table II. Patients treated with interferon beta.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Histology</th>
<th>Contagion</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 females</td>
<td>60-75</td>
<td>cae = 9 cases</td>
<td>post-transfusion = 10 cases</td>
</tr>
<tr>
<td>7 males</td>
<td></td>
<td>pce = 4 cases</td>
<td>unknown = 3 cases</td>
</tr>
</tbody>
</table>

Patients treated with non-specific therapy

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Histology</th>
<th>Contagion</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 females</td>
<td>65-72</td>
<td>cae = 6 cases</td>
<td>post-transfusion = 7 cases</td>
</tr>
<tr>
<td>5 males</td>
<td></td>
<td>pce = 7 cases</td>
<td>unknown = 6 cases</td>
</tr>
</tbody>
</table>

cae = chronic active hepatitis; pce = persistent chronic hepatitis.
Results

1. In patients of the I study, at the end of treatment, the results showed the following: ALT and AST normalisation in 15 out of 20 treated patients (75%) with ALT mean values of 38U/l compared to initial mean values of 231 U/l and unsatisfactory response in 5 patients (Figure 1).

At the histologic check-up performed at the end of therapy it was found that there was a regression of lobular inflammation in 11 responders and in 2 non responders (65%) as well as disappearance of the phlogogenous infiltrate and of necrosis in 1 patient.

The most frequently observed side-effects in patients belonging to this study were:

- hyperthermia and arthromyalgia in 18/20 patients following to the first 4-5 drug administrations;
- weight loss (3-4 kg) in all patients;
- platelet disorder and reduction of leukocytes in 3 patients.

No case required the interruption of the therapy.

2. In patients of the II study, at the end of treatment, results showed the following: ALT and AST normalisation in 7/13 patients treated—

\[
\text{Table III. Patients treated with lymphoblastoid interferon.}
\]

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Histology</th>
<th>Contagion</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 females</td>
<td>62-74</td>
<td>cae = 41 cases</td>
<td>post-transfusion = 27 cases</td>
</tr>
<tr>
<td>28 males</td>
<td></td>
<td>pce = 9 cases</td>
<td>unknown = 23 cases</td>
</tr>
</tbody>
</table>

Patients treated with non-specific therapy

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Histology</th>
<th>Contagion</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 females</td>
<td>60-72</td>
<td>cae = 35 cases</td>
<td>post-transfusion = 32 cases</td>
</tr>
<tr>
<td>29 males</td>
<td></td>
<td>pce = 15 cases</td>
<td>unknown = 18 cases</td>
</tr>
</tbody>
</table>

cae = chronic active hepatitis; pce = persistent chronic hepatitis.

The most frequently observed side-effects in patients belonging to this study were:

- hyperthermia and arthromyalgia in 18/20 patients following to the first 4-5 drug administrations;
- weight loss (3-4 kg) in all patients;
- platelet disorder and reduction of leukocytes in 3 patients.

No case required the interruption of the therapy.

2. In patients of the II study, at the end of treatment, results showed the following: ALT and AST normalisation in 7/13 patients treat-
ed with IFN beta (53.8%) with ALT mean values of 34 U/l compared to initial mean values of 265 U/l, whereas 6 patients were non responders (Figure 2).

The histological check-up showed a reduction of the phlogosis in 8 patients (61%) – 6 responders and 2 non responders – as well as disappearance of the phlogogenous infiltrate and of the membrane necrosis in one patient. No cases of hyperthermia, arthromyalgia, platelet disorder or reduction of leukocytes were detected.

3. As far as the III study is concerned, 30/50 patients treated with lymphoblastoid IFN (60%) showed ALT normalisation with ALT mean values of 36 U/l compared to initial mean values of 233 U/l (Figure 3), whereas only two of the patients treated with non-specific therapy showed transaminase normalisation.

Histological evaluation performed in this study showed an improvement in the clinical picture in 22 responders and in 6 non responders (56%). No improvement of the histological picture was noticed in the group of patients subjected to non-specific therapy.

The most frequent side-effects found in this study were:
- influenza-like syndrome in 38 patients;
- weight loss (5-6 kg), weakness, anorexia, general discomfort in all patients;
- leukopenia and/or platelet disorder in 24 patients, but the values were such as it was not necessary to suspend the therapy.

The Table IV shows, in synthesis, the main side-effects during therapy with the various types of interferon.

A follow up without treatment was performed at the end of therapy for all responders. At the end of this period, evaluated in one year, the maintenance percentage of response varied from 43% (for patients treated with b-interferon) to 60% (for patients treated with lymphoblastoid interferon). For the patients treated with recombinant interferon 2b no follow up period was scheduled.

An increase in the values of transaminase began to appear already in the first weeks immediately after interruption of therapy.

**Conclusion**

HCV correlated chronic hepatitis, though resulting in a high percentage of cases of cirrhosis, is characterised by a slow evolution.
Also, the functional disorder and serious complications deriving from it can be observed only after several years\textsuperscript{16-17}. It is because of such slow evolution of chronic hepatitis C and owing to the serious side-effects linked to interferon that not all the authors agree to treat elderly patients with this drug. However, this drug nowadays represents the only therapy whose efficacy in the treatment of HCV correlated chronic hepatitis has been demonstrated\textsuperscript{10}.

This study proves that elderly patients suffering from HCV correlated chronic hepatitis respond to treatment with different types of interferon, though in a sufficiently diversified way, and their percentages of remission are similar to those verified in studies on young and adult patients\textsuperscript{18-29}. As a matter of fact, the three studies analysed in this paper are not comparable since they present remarkable differences: number of patients, length of treatment, the way the single studies were conducted. In fact, the results of the present work point out a certain difficulty in establishing a single and homogeneous therapeutic scheme as well as an easy and simple interpretation of the results. These latter, however, tend to highlight the possibility or even so the necessity to resort to interferon therapy on patients aged above 65, since their life expectancy is sufficiently long\textsuperscript{11}.

While evaluating the results taken into examination in the present study, one has to consider that the subtype 1b of HCV, which is the most frequently found in the area where we work, is also the one which is usually the most resistant to interferon therapy. Therefore, a careful and thorough clinical evaluation of therapeutic effects with various types of interferon cannot leave out of consideration the link existing between the effects of therapy, 1b genotype, the potential evolutionary process of the disease and the prognostic value of it\textsuperscript{9}.

In spite of these aspects, as noticeable from the results, both recombinant interferon alpha 2b and interferon beta as well as the lymphoblastoid interferon present rather high remission percentages and, however, comparable to what highlighted in other studies conducted on young adult patients\textsuperscript{18-29}.

Furthermore, taking into account the results obtained in the above mentioned experiences, that is to say at the end of treatment

Figure 3. Mean ALT levels in the study-group.
period with recombinant interferon alpha 2b and β-interferon and lymphoblastoid interferon the remission percentages were found to be respectively 75%, 53.8% and 60%. Thus, the recombinant interferon alpha is preferable when treating this pathology in elderly patients.

On the other hand, a more articulate interpretation is necessary as far as the evaluation of side-effects linked to interferon therapy is concerned. As a matter of fact, the most remarkable differences in the results arise exactly when considering side-effects (Table IV). When comparing these studies it is possible to infer that the recombinant interferon alpha seems to cause most side-effects, whereas β-interferon is virtually safe. In our opinion, this raises an interesting debate with regard to the choice and the use of the various types of interferon in the geriatric field. In fact, as a result of our experience, on the one hand interferon alpha seems the most desirable by virtue of higher response percentages, on the other hand, the lack of side-effects in interferon beta seems to suggest the utilisation of the latter. As a matter of fact, our data showed that side-effects were never so serious as to justify interruption of therapy. Therefore, in a global evaluation of the risk/benefit ratio INF alpha should be preferred in the treatment of elderly patients suffering from HCV correlated chronic hepatitis.

Another interesting problem which arises in the treatment of the elderly is the relapse of the disease which often occurs after the interruption of interferon therapy and it is probably linked to the persistence of viremia in extrahepatic organs after the scheduled therapy course.

If this happens our suggestions basically include two hypotheses of treatment:

- to make use of therapy schemes which include higher initial doses than the ones usually administered, since these are able to start an “evoked response” to therapy;
- to prolong the treatment period beyond the first scheduled year and continue for at least six months with minimum efficacious dose able to keep up the response. This will result in a further improvement of the histological picture, independently from the humoral picture.

In the light of what exposed above, it is now possible to state that our data are not homogeneous. The most remarkable differences are relative both to the side-effects provoked by the various types of interferon and to the normalisation of the humoral picture, whereas the differences relative to the histological picture were less remarkable.

Lastly, the cost/benefit analysis of the various treatments must also be considered. When comparing the response percentages obtained in the various studies, side-effects and the cost of each single therapeutic cycle, the best cost/benefit ratio seems to be favourable to recombinant interferon alpha.

However, it is important to stress that no case required interruption of the therapy, in spite of serious side-effects. This enables us to affirm that even when there is a higher exposure to side-effects linked to the use of recombinant interferon alpha, still, the risk/benefit ratio suggests the use of this particular drug for the treatment of this pathology in elderly patients.

<table>
<thead>
<tr>
<th></th>
<th>rec IFN</th>
<th>β IFN</th>
<th>lym IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>% influenza-like syndrome</td>
<td>90%</td>
<td>no</td>
<td>76%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>100%</td>
<td>no</td>
<td>100%</td>
</tr>
<tr>
<td>% reduction of PLT and/or WBC</td>
<td>35%</td>
<td>no</td>
<td>48%</td>
</tr>
</tbody>
</table>

rec IFN = recombinant interferon; lym IFN = lymphoblastoid interferon.
Different types of interferon for the therapy of HCV chronic active hepatitis

References


