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Different types of interferon for the therapy of HCV chronic active hepatitis in the elderly patient

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Abstract. – HCV correlated hepatitis is a pathology on the increase, and it is especially affecting patients above 60 years old. The only treatment for this disease is therapy with different types of interferon.

The authors take into examination three of their previous studies on treatment of HCV correlated chronic hepatitis in the elderly using different types of interferon: recombinant interferon alpha, interferon beta, and lymphoblastoid interferon, in order to evaluate which one, among the three, should be the best for the treatment of this pathology in the elderly.

The data show that recombinant interferon alpha is preferable since the remission percentage is higher (75%), compared to beta (53.8%) and lymphoblastoid interferon (60%).

As far as the relevant side-effects in elderly patients are concerned, beta-interferon therapy is almost with no side-effects. Even in cases where there could be a possible higher exposure to side-effects linked to the use of recombinant interferon alpha, still, the risk/benefit ratio suggests that this particular drug should be used for treating this pathology in elderly patients.

Key Words:

Chronic hepatitis, Interferon, Elderly.

Introduction

HCV correlated chronic hepatitis is on the increase, especially in elderly patients. The infection seems to be to a great extent age-correlated, since it primarily affects elderly patients aged above 65[1-3]. Besides, it has been observed that among hospitalised patients 40% of patients with HCV infection is above 65. Also, a predominance of HCV positive health care staff in the geriatric department has been remarked in comparison with other health care workers[4].

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[5-7].

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[8]. 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[9].

At present the only therapy whose therapeutic efficacy has been demonstrated for the treatment of chronic hepatitis C is represented by interferon[10].

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)[11]. 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

Table I. Patients treated with recombinant interferon alpha.

Patients	Age	Histology	Contagion
6 females	60-69	cae = 11 cases	transfusion = 11cases
14 males		pce =7 cases n.b. = 2 cases	unknown = 9 cases

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

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[12-14].

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

I) The first study[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[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 β-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 β-IFN given in alternate evenings for two months and later on for other 10 months 6MU via IM of β-IFN were given in alternate evenings.

III) The third study[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[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 II. Patients treated with interferon beta.

Patients	Age	Histology	Contagion
6 females	60-75	cae = 9 cases	post-transfusion = 10 cases
7 males		pce = 4 cases	unknown = 3 cases
		Patients treated with non-specific therapy	
8 females	65-72	cae= 6 cases	post-transfusion = 7 cases
5 males		pce= 7 cases	unknown= 6 cases

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

Table III. Patients treated with lymphoblastoid interferon.

Patients	Age	Histology	Contagion
22 females	62-74	cae = 41 cases	post-transfusion = 27 cases
28 males		pce = 9 cases	unknown = 23 cases
Patients treated with non-specific therapy			
21 females	60-72	cae= 35 cases	post-transfusion = 32 cases
29 males		pce= 15 cases	unknown= 18 cases

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 treat-

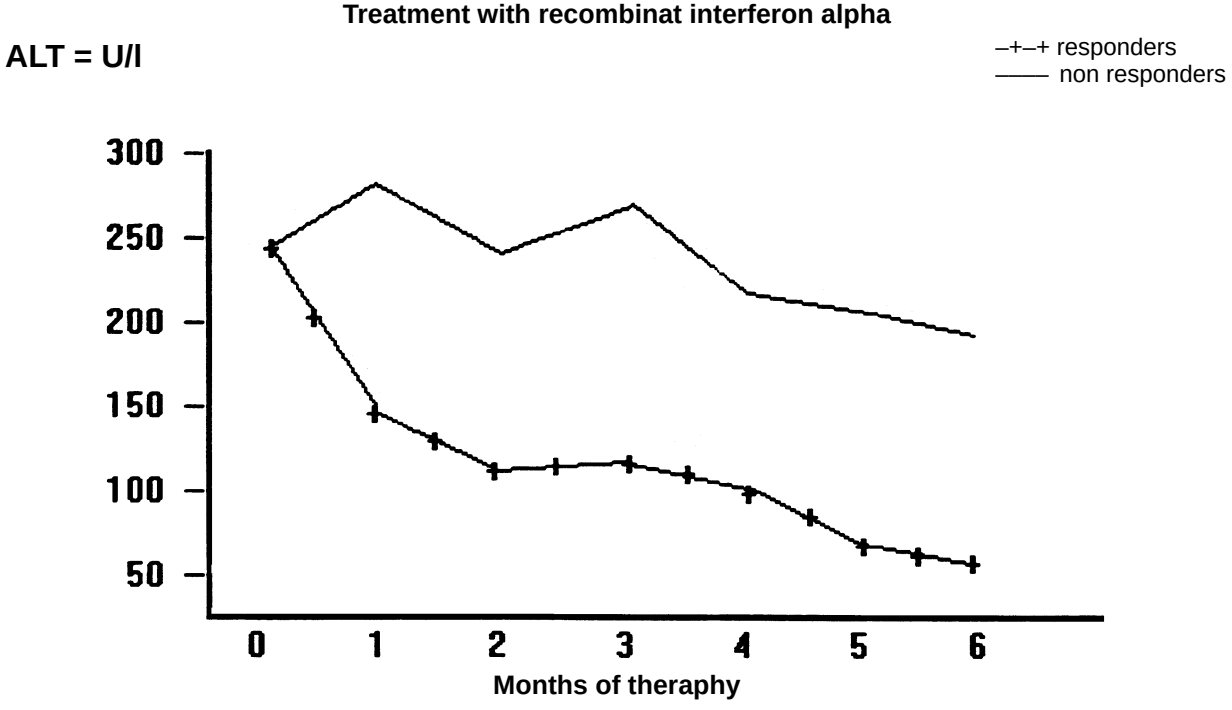

Figure 1. Mean ALT levels in the patients included in the study.

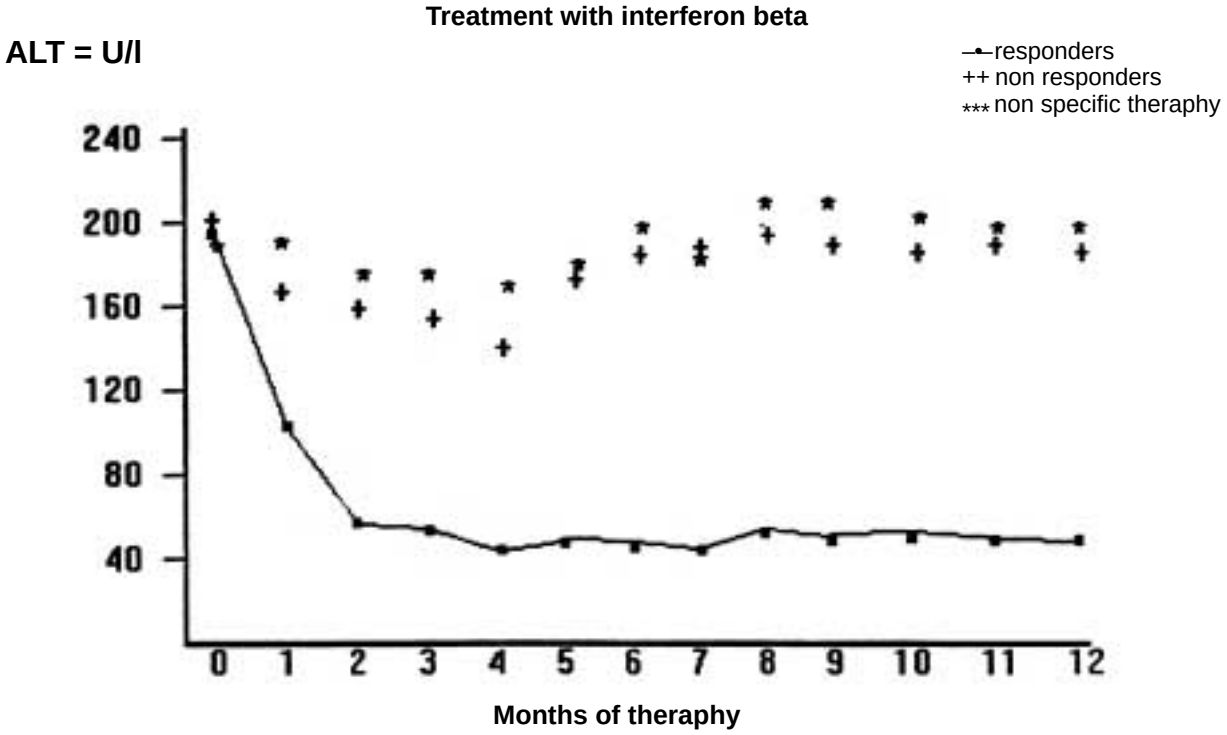

Figure 2. Mean ALT levels in the study-group.

ed with IFN beta (53.8%) with ALT mean values of 34 U/l compared to initial mean values of 265U/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 36U/l compared to initial mean values of 233U/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.

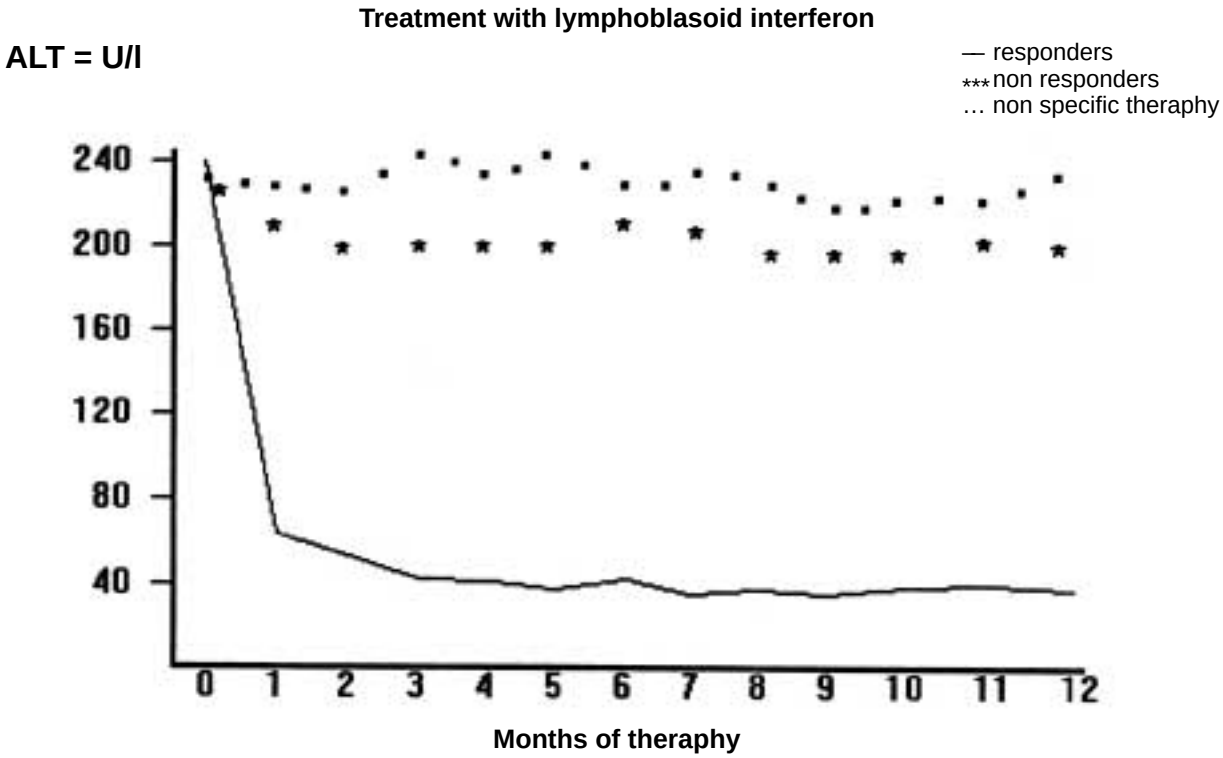

Figure 3. Mean ALT levels in the study-group.

Also, the functional disorder and serious complications deriving from it can be observed only after several years[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[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[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[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[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[18-29].

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

Table IV. Main side-effects found in the three studies.

	rec IFN	β IFN	lym IFN
% influenza-like syndrome	90%	no	76%
Weight loss	100%	no	100%
% reduction of PLT and/or WBC	35%	no	48%

rec IFN = recombinant interferon; lym IFN = lymphoblastoid interferon.

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 b-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[30].

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[31-33];
- 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.

References

1) Sirchia G, Bellobuono A, giovanetti A, Marconi M. Antibodies to hepatitis C virus in Italian blood donors. Lancet 1989; 30: 797.

2) Janot C, Couroucé AM, Maniez M. Antibodies to hepatitis C virus in French blood donors. Lancet 1989; 30: 796-797.

3) Stevens C, Taylor PE, Pindyck J, Choo QL, Bradley DW, Kuo G, Houhton M. Epidemiology of hepatitis C. A preliminary study in volunteer blood donors. JAMA 1990; 263: 49-53.

4) Hofmann H, Kunz C. Low risk of health care workers for infection with hepatitis C virus. Infection 1990; 5: 286-288.

5) Seeff LB. Natural history of hepatitis C. Hepatology 1997; 26 (Suppl 1): 21S-28S.

6) Colombo M, De Franchis R, Del Ninno E et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991; 325: 675-680.

7) Gentilini P, Laffi G, La Villa G et al. La cirrosi epatica virus-correlata: storia naturale, patogenesi e implicazioni cliniche delle complicanze. Ann Ital Med Int 1996; 11: 523-529.

8) Simmonds P, Alberti A, Alter HS. A proposed system for the nomenciature of hepatitis C viral genotypes. Hepatology 1994; 19: 1321-1324.

9) Associazione Italiana Studio Fegato. Diagnostica molecolare nell'infezione da HCV: applicazioni nella pratica clinica. Notiz Ist Sup di Sanità. 1996; 9: 1-12.

10) Balsano C, Artini M, Giambartolomei S, Almerighi C. Terapia dell'epatite da virus C. Trattamenti convenzionali e non. G. Gastroenterol 1997; 3: 130-137.

11) Associazione Italiana Studio Fegato. Linee guida per il trattamento delle epatiti croniche virali. 1997; 1: 1-11.

12) Terranova R, Luca S, Dimora AL. Epatite cronica C nell'anziano. Valutazione del trattamento con interferone alfa ricombinante. G Gerontol 1991; 39: 63-67.

13) Terranova R, Luca S. Preliminary results of beta-interferon treatment in the elderly. Controll Clin Trials 1996; 17: 123-129.

14) Terranova R, Luca S. Treatment of chronic hepatitis C with lymphoblastoid interferon alpha in eldely patients. Eur Rev Med Pharmacol Sci 1997; 1: 47-52.

15) Knodell RG, Ishak KG, Black WC et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981; 1: 431-435.

16) Seeff LB, Buskell-Bales Z, Wright EC et al. Long term mortality after transfusion associated nonA-nonB hepatitis. N Engl J Med 1992; 327: 1906-1911.

17) Koretz RL, Absey H, Coleman E, Gitnick G. NonA-nonB post-transfusion hepatitis. Ann Intern Med 1993; 119: 110-115.

18) Marcellin P, Boyer N, Martinot M et al. Comparison de l'effet de l'interferon gamma et de l'interferon alpha sur le taux serique des aminotransferases alt dans l'hepatite chronique non A non B. Gastroenterol Clin Biol 1989; 13: 173.

19) Bardelli F, Messori A, Rampazzo R et al. Effect of recombinant or lymphoblastoid interferon-a on alanine aminotransferase in patients with chronic hepatitis C or chronic nonA-nonB hepatitis. A meta- analysis. Clin Drug Invest 1995; 9: 239-254.

20) Gomez-Rubio M, Porres JC, Castillo I, Quiroga JA, Moreno A, Carreno V. Prolonged treatment (18 months) of chronic hepatitis C with recombinant alpha-interferon in comparison with a control group. J Hepatol 1990; 11 (Suppl 1): S63-S67.

21) Schvarz R, Weiland O, Weijstal R et al: Treatment of chronic post-transfusion nonA-nonB hepatitis with interferon alfa-2b. J Hepatol 1989; 9 (Suppl 1): S224-228.

22) Bacon BR, Farrell G, Benhamou JP et al. Lymphoblastoid interferon improves long-term response to a six month course of treatment when compared with recombinant interferon alfa- 2b: results of an international trial. Hepatology 1995; 22: 152A.

23) Davis GL, Balart L, Schiff E, Lindsay K, Bodenheimer HC Jr et al. Treatment of chronic hepatitis C with recombinant interferon alpha. A multicenter randomized controlled trial. Hepatitis Interventional Therapy Group. N Engl J Med 1989; 321: 1501-1506.

24) Weiland O, Schvarz R, Weijstal R, Norkrans G et al. Interferon alpha 2b treatment of chronic post-transfusion nonA-nonB hepatitis: interim results of a randomized controlled open study. Scand J Infect 1989; 21: 127-132.

25) Nakano Y, Kiyosawa K, Sodeyama T, Tanaka E. Comparative study of clinical, histologic and immunologic response to ìnterferon therapy in type nonA-nonB and type B chronic hepaiítis. Am J Gastroent 1990; 85: 24-29.

26) Terranova R, Luca S. Trattamento dell'epatite cronica C con interferone alfa ricombinante. Rass Med Int 1990; 11: 333-338.

27) Terranova R, Luca S. Treatment of chronic hepatitis C with recombinant interferon alpha 2b. J Chemother 1992; 4: 297-302.

28) Arima T, Shimoimura H, Nakagawa G. Treatment of nonA-nonB hepatitis with human fibroblast interferon. Hepatology 1986; 6: 1117-1121.

29) Nishiguchi S, Kuroki T, Hirota S et al. Interferon (IFN) therapy for chronic nonA-nonB hepatitis. Gastroenterology 1989; 95: A577.

30) Associazione Italiana Studio Fegato. Terapia dell'epatite cronica C. In Atti del Convegno Nazionale Taormina 1997, 28 Feb-2 Mar.

31) Chemello L, Bonetti P, Cavalletto L et al. Randomized trial comparting three different regimens of (α 2a interferon in chronic hepatitis C. The Triveneto Viral Hepatitis Group. Hepatology 1995; 22: 700-706.

32) Poynard T, Bedossa P, Chevailler M et al. A comparison of three interferon α 2a regimens for the long term treatment of chronic nonA-nonB hepatitis. N Engl J Med 1995; 332: 1457-1462.

33) Poynard T, Leroy V, Cohard M et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996; 24: 778-789.