Rev. Inst. Med. trop. São Paulo
37 (3): 239-243, maio/junho, 1995.

LONG TERM FOLLOW-UP AND PATTERNS OF RESPONSE OF ALT IN PATIENTS WITH CHRONIC HEPATITIS NANB/C TREATED WITH RECOMBINANT INTERFERON-α

L.C. da SILVA, S.K. ONO, L.E.P. FONSECA, F.J. CARRILHO, L.C.A. MENDES, A.V.C. FRANÇA, C.L.A. MADRUGA & A.A. LAUDANNA

SUMMARY

The response to interferon treatment in chronic hepatitis NANB/C has usually been classified as complete, partial or absent, according to the behavior of serum alanine aminotransferase (ALT). However, a more detailed observation of the enzymatic activity has shown that the patterns may be more complex. The aim of this study was to describe the long term follow-up and patterns of ALT response in patients with chronic hepatitis NANB/C treated with recombinant interferon-α. A follow-up of 6 months or more after interferon-α was achieved in 44 patients. We have classified the serum ALT responses into six patterns and the observed frequencies were as follows: I. Long term response = 9 (20.5%); II. Normalization followed by persistent relapse after IFN = 7 (15.9%); III. Normalization with transient relapse = 5 (11.9%); IV. Temporary normalization and relapse during IFN = 4 (9.1%); V. Partial response (more than 50% of ALT decrease) = 7 (15.9%); VI. No response = 12 (27.3%). In conclusion, ALT patterns vary widely during and after IFN treatment and can be classified in at least 6 types.

KEYWORDS: . Chronic hepatitis; Hepatitis C; Antiviral Therapy; Interferon; Response; Relapse.

INTRODUCTION

Chronic hepatitis C (CH-C) ranks as one of the most important causes of chronic liver disease, cirrhosis and hepatocellular carcinoma. Typically, CH-C is a prolonged and insidious disease marked by persistent elevations of serum aminotransferases. Therefore, this disease warrants a specific and effective therapy. At present, however, the only agent of proven benefit is alpha-IFN.

The current recommendations for therapy of hepatitis C are a 6-month course of α-interferon (IFN) in doses of 3 million units 3 times weekly and the long-term beneficial response to IFN occurs in only 10 - 25% of patients [8]. There have been numbers of clinical trials evaluating the efficacy of recombinant α-interferon treatment of chronic hepatitis C [3, 4, 9] and the predictive factors of response [1, 10, 13, 16, 18]. However, the response definitions vary in each study.

Unfortunately, most studies of IFN in CH-C found a very high relapse rate once therapy was stopped. Furthermore, a detailed analysis of serum ALT levels during and after IFN has shown a variable pattern with different clinical and prognostic meanings.

Our aim was to study the long term follow-up and the types of ALT response in 44 patients with chronic hepatitis NANB/C treated with IFN, specifically describing and discussing these patterns.

List of abbreviations: IFN Interferon; ALT Alamineaminotransferase; NANB/C Non A- Non B/C; CH-C Chronic hepatitis C; HCV Hepatitis C virus and PCR Polymerase chain reaction.

Departament of Gastroenterology - Hepatology branch, University of São Paulo, School of Medicine; Institute of Tropical Medicine (LIM-47) São Paulo, SP, Brazil.

Correspondence to: Prof. Luiz Caetano da Silva, Instituto de Medicina Tropical, Av. Dr. Enéas de Carvalho Aguiar, 470, 05403-000 São Paulo, SP, Brasil. Telephone number: (011) 883-3233 ramal 328

PATIENTS AND METHODS

We studied 44 adults who had had persistently elevated serum alanine aminotransferase levels (at least 1 1/2 times the upper limit of normal range). Because no serologic assays for hepatitis C virus (HCV) were available when the study began, 19 patients who were clinically and histologically diagnosed as having non-A, non-B (putative HCV) chronic hepatitis, who were known not to have hepatitis B, alcoholic liver disease, a drug induced hepatic disorder or autoimune hepatic disease were enrolled in the study. Of these 19 patients, serology was performed after treatment in 15, with a positive anti-HCV in 11 patients. After 1991, 25 subjects had the serum tested for the presence of antibody to HCV before the treatment was instituted and all were shown to be positive. A liver biopsy was obtained in 41 subjects.

Patients received 3 million units 3 times weekly for 6 months, followed by 1,5 million units 4 times weekly for an additional 6 months, in case of complete normalization of serum ALT. Prophylactic antipyretic drugs were given soon after IFN injection to relieve the flulike syndrome associated with IFN therapy.

Biochemical assesment of liver injury, defined by serum alanine transferase and peripheral blood counts were obtained monthly during and for at least 6 months after finishing the treatment.

Patients were classified into six groups, according to their ALT response: I. Long term response, defined as the normalization of the ALT by the end of the treatment and its persistence after interruption of IFN; II. Normalization followed by persistent relapse, defined as a persistent increase of serum ALT level to more than 1 1/2 times the upper normal limit after IFN; III. Normalization with transient relapse, defined as a normalization of the ALT levels by the end of treatment with a transient increase of the ALT level to more than 1 1/2 times the upper limit of normal; IV. Temporary normalization and relapse of ALT during the treatment with IFN ("breakthrough"); V. Partial response, defined as a decrease of ALT levels to less than 50% of the initial level and VI. No response, when the above mentioned changes have not been observed.

RESULTS

The six patterns described are illustrated in Figure 1-6. Nine of 44 patients (20.5%) showed a long-term

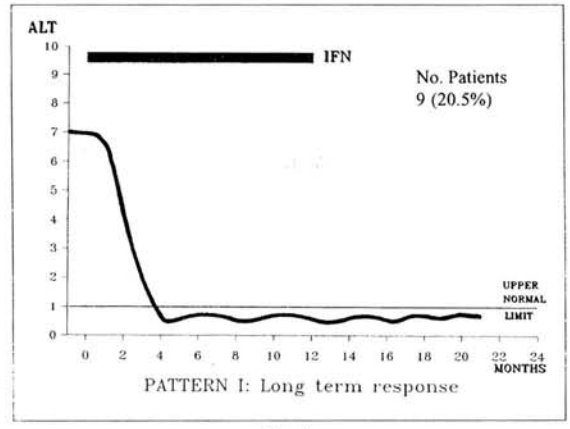

Fig. 1

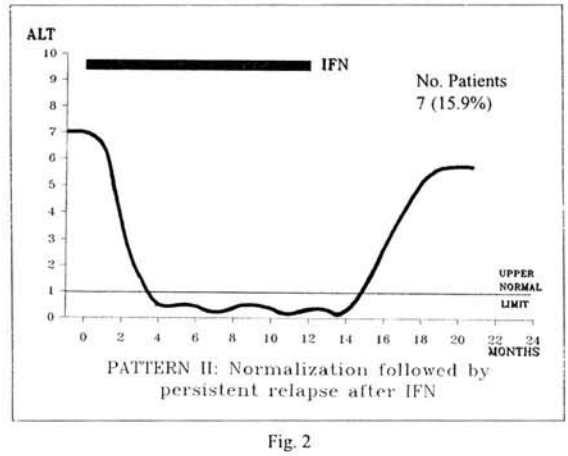

Fig. 2

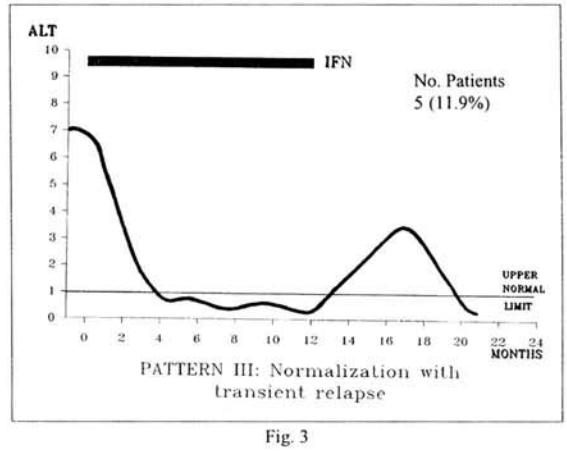

Fig. 3

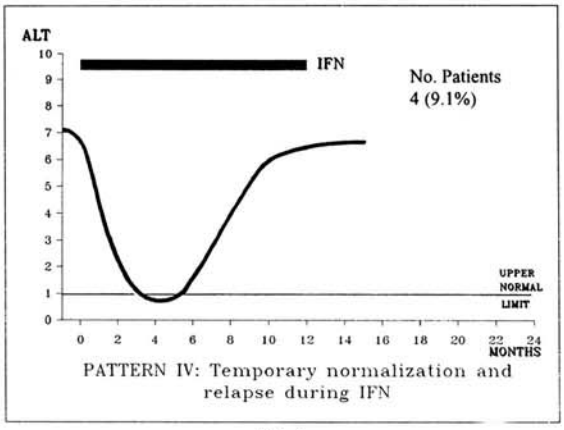

Fig. 4

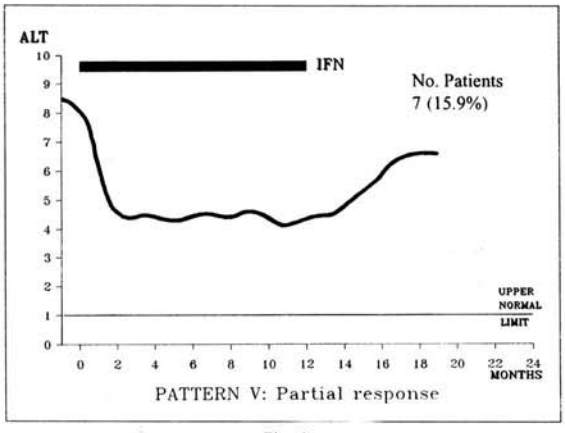

Fig. 5

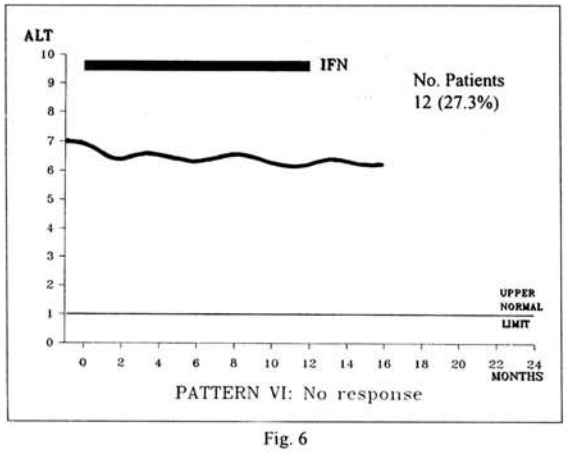

Fig. 6

response (pattern I). Seven (15.9%) had a pattern II response. The third pattern was observed in five (11.3%) patients, and in two of them an exogenous factor responsible for the relapse was identified (cocaine and endocarditis). The number of patients with pattern IV, V and VI were respectively 4 (9.1%), 7 (15.9%) and 12 (27.3%).

DISCUSSION

In this study, we focused our attention on the curves of ALT levels during and after the IFN treatment.

In pattern I, the mechanism explaining this kind of response is the disappearance of the HCV RNA, although some subjects with the long-term response evaluated by the ALT and by histologic remission could maintain a positive PCR, suggesting a possible selection of non-pathogenic serological typing of HCV or a replication of the virus outside of the liver [2]. In our study, this pattern was observed in 9/44 (20.5%) patients. These patients should be seen every 3 months with ALT serum and RNA-VHC determinations. Follow-up liver biopsies should be considered after 6 to 12 months after IFN.

Reappearance or increase of viremia, HCV mutation and other reasons non-related to HCV could explain pattern II of response, observed in 7/44 patients (15.9%). Furthermore, a recent article by FARCI et al. [5], based on re-infections in the chimpanzee, concluded that HCV infection does not elicit protective immunity against re-infection with homologous or heterologous strains. SHAPIRO [17] raised interesting questions related to the hemophilic patient population, for example, whether patients who are infected with HCV are susceptible to reinfection and if it is possible to differentiate between HCV reactivation and reinfection. Although none of our patients were hemophiliacs or were exposed to a frequent source of infection it is debatable whether a relapse could be a reinfection, a reactivation, due to HCV mutant or to other reasons non-related with HCV. This pattern of response deserves further investigation, but in any case a 6 month period of expectation is recommended. If relapse is persistent, retreatment with IFN or its association to ribavirin should be considered.

Pattern III (11.9%), might be due to spontaneous fluctuation of serum ALT and of the HCV-RNA levels

or to other reasons non-related to HCV. This pattern was observed in five of our patients. In one, the increase of the ALT was due to bacterial endocarditis which was treated and followed by normalization of the ALT. Another patient had a cocaine endovenous intoxication previously to the ALT relapse, which normalized afterwards. This patient had a second relapse after another cocaine intoxication [12]. Patients with this kind of ALT pattern should be observed during 6 months and if normalization is persistent and accompanied by the negativation of HCV RNA, the same management as indicated in pattern I should be adopted.

Temporary normalization and relapse during IFN treatment ("breakthrough", pattern IV = 9.1%) could be explained by the appearance of anti-interferon antibodies particularly in patients treated with IFN alfa-2a [11], by the exacerbation of an autoimmune hepatitis [14], by the mutation of HCV [19] or, perhaps by a spontaneous oscilation of ALT. These patients should have their IFN discontinued and the problem of autoimmune disorders reconsidered. In those patients who develop anti-interferon antibodies, IFN should be withdrawed or substituted by another type of IFN (e.g. lymphoblastoid or beta interferon).

Partial reduction of HCV-RNA levels or a lower sensitivity of HCV to IFN could explain the partial response (pattern V = 15.9%). In this case, an increase of the dose of IFN or its association to ribavirin should be considered.

Different viral strains resistant to IFN or mutant HCV are possible mechanisms for the lack of response observed in 12/44 patients (27.3%). In this regard, HCV genotype 1b or type II of Okamoto is considered more resistant to IFN [15]. Treatment of these patients is rather difficult, as only a few respond to an increase of dosage [6]. According to HOOFNAGLE [7] "treatment should be stopped early - after 2-3 months - in these patients, and they should not be given higher doses or repeated courses".

Although six patterns were well characterized in this study we would like to call attention for the possibility of another pattern represented by the normalization of ALT after a complete course of IFN is given ("late response"). This pattern was observed in one patient.

In summary, the analysis of the ALT curves gives us interesting clues about the biological behavior of the HCV to treatment with IFN and could help to decide on further recommendations for the therapy of chronic hepatitis C.

RESUMO

Seguimento tardio e padrões de resposta da ALT em pacientes com hepatite crônica NANB/C tratados com interferon-α.

A resposta ao tratamento com interferon em pacientes com hepatite crônica NANB/C tem sido classificada como completa, parcial ou ausente, de acordo com o comportamento da alanino aminotransferase sérica (ALT). Entretanto, uma observação mais detalhada da atividade enzimática tem mostrado que os padrões podem ser mais complexos. O objetivo deste estudo foi descrever o seguimento tardio e os padrões de resposta da ALT em pacientes com hepatite crônica NANB/C tratados com interferon alfa recombinante. Classificamos os tipos de resposta da ALT em 6 padrões e as freqüências observadas foram:I. Resposta completa e persistente = 9 (20,5%); II. Resposta completa com recaída persistente após o IFN = 7 (15,9%); III. Resposta completa com recaída temporária = 5 (11,9%); IV. Normalização temporária e recaída durante o tratamento com IFN = 4 (9,1%); V. Resposta parcial (queda dos níveis iniciais da ALT maior que 50%) = 7 (15,9%); VI. Não resposta = 12 (27,3%). Em conclusão, os padrões de ALT variam durante e após o tratamento e podem ser classificados em pelo menos 6 tipos.

ACKNOWLEDGEMENT

The authors would like to thank Dr. Marcos Wolff for reading this manuscript and making a number of valuable suggestions. Dr. S.K. Ono was a recipient of a grant supported by Schering-Plough Laboratories.

REFERENCES

1. ALBERTI, A.; CHEMELLO, L.; BONETTI, P. et al. - Treatment with interferon(s) of community-acquired chronic hepatitis and cirrhosis type C. **J. Hepat., 17** (suppl. 3): S123-S126, 1993.

2. BONINO, F.; BRUNETTO, M.R.; NEGRO, F. et al. - Hepatitis C virus infection and disease. Diagnostic problems. **J. Hepat., 17** (suppl. 3): S78-S82, 1993.

3. DAVIS, G.L.; BALART, L.A.; SCHIFF, E.R. et al. - Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial. **New Engl. J. Med., 321**:1501-1506, 1989.

4. DOUGLAS, D.D.; RAKELA, J.; LIN, H. J. et al. - Randomized controlled trial of recombinant alpha-2a-interferon for chronic hepatitis C. Comparison of alanine aminotransferase normalization versus loss of HCV RNA and anti-HCV IgM. **Dig. Dis. Sci., 38**: 601-607, 1993.

5. FARCI, P.; ALTER, H. J.; GOVINDARANJAN, S. et al. - Lack of protective immunity against reinfection with hepatitis C virus. **Science, 258**: 135-140, 1992.

6. FONSECA, L.E.P. da. - *Tratamento da hepatite crônica não-A, não-B com interferon - alfa recombinante.* São Paulo 1992. (Dissertação de mestrado - Faculdade de Medicina da Universidade de São Paulo).

7. HOOFNAGLE, J.H. - Treatment. **In**: ZUCKERMAN, A.J. & THOMAS, H.C. Viral hepatitis. Scientific basis and clinical management. Edinburgh, Churchill Livingstone, 1993. p. 307.

8. HOOFNAGLE, J. H.; DI BISCEGLIE, A.M. & SHINDO, M. - Antiviral therapy of hepatitis C - present and future. **J. Hepat., 17** (suppl. 3): S130-S136, 1993.

9. IINO, S.; HINO, K.; KUROKI, T.; SUZUKI, H. & YAMAMOTO, S. - Treatment of chronic hepatitis C with high-dose Interferon a-2b. A multicenter study. **Dig. Dis. Sci., 38**: 612-618, 1993.

10. JOUET, P.; ROUDOT-THOROVAL, F.; DHUMEAUX, D.; MÉTREAU, J.M. & Le Group Français pour létude du traitment des hépatites chroniques NANB/C - Comparative efficacy of interferon alfa in cirrhotic and noncirrhotic patients with non-A, non-B, C hepatitis. **Gastroenterology, 106**: 686-690, 1994.

11. MILLELA, M.; ANTONELLI, G.; SANTANTONIO, T. et al. - Neutralizing antibodies to recombinant alpha-interferon and response to therapy in chronic hepatitis C virus infection. **Liver, 13**: 146-150, 1993.

12. ONO, S.K.; MENDES, L.C.A.; DA SILVA, L.C. et al. - Cocaína como causa de "recaída" após interferon alfa recombinante (IFN) na hepatite C. **In**: CONGRESSO BRASILEIRO DE GASTROENTEROLOGIA., 33, Porto Alegre, 20-23 de novembro de 1994.

13. ORITO, E.; MIZOKAMI, M.; MIZOGUCHI, N. et al. - Hepatitis C virus serotype II responds more favorably to interferon-a therapy. **J. Hepat., 21**: 130-132, 1994.

14. PAPO, T.; MERCELLIN, P.; BERNUAU, J. et al. - Autoimmune chronic hepatitis exacerbated by Alpha-Interferon. **Ann. intern. Med., 116**: 51-53, 1992.

15. QU, D.; LI, J. S.; VITVITSKI, L. et al. - Hepatitis C virus genotypes in France: comparison of clinical features of patients infected with HCV type I and type II. **J. Hepat., 21**: 70-75, 1994.

16. SERFATY, L.; GIRAL, P.; LORIA, A. et al. - Factors predictive of the response to interferon in patients with chronic hepatitis C. **J. Hepat., 21**: 12-17, 1994.

17. SHAPIRO, A. - Long term surveillance of HIV, HBV and HCV infected patients. **Ann. Hematol., 68**: S87-S88, 1994.

18. VAN THIEL, D. H.; FRIEDLANDER, L.; FAGIUOLI, S. et al. - Response to interferon α therapy is influenced by the iron content of the liver. **J. Hepat., 20**: 410-415, 1994.

19. YOSHIOKA, K.; KAKAMU, S.; AIYAMA, T. - Detection of serum antibodies to E2/NS1 hypervariable region of hepatitis C virus. **Hepatology, 20**: 231A, 1994.

Recebido para publicação em 26/12/1994.
Aceito para publicação em 07/03/1995.