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TREATMENT OF PATIENTS WITH CHRONICAL HEPATITIS C (1b) WITH NORMAL AND ELEVATED ALT

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Abstract

Aim: The aim of the study was the evaluation of treatment with Pegasys Interferon/Copegus for 48 weeks in patients with elevated and normal ALT in the beginning of it.

Patients and methods: 33 pts with chronical hepatitis C, 1b were included in this study (18 M, 15 F, mean age 39.2 yr., diagnosed and treated during 2008 - 2010). Before the beginning of treatment the pts were divided in two groups: 1. with elevated ALT (19) and 2. with normal ALT (14). Treatment: Pegasys INF 180 μg/w and Copegus 1000 – 1200 mg/d for 48 weeks. Clinical, biological and virological examination of pts was performed before treatment and in weeks 4, 12, 24, 48 and 72. Sustained virological response was considered the situation with negative HCV RNA, 24 weeks after treatment.

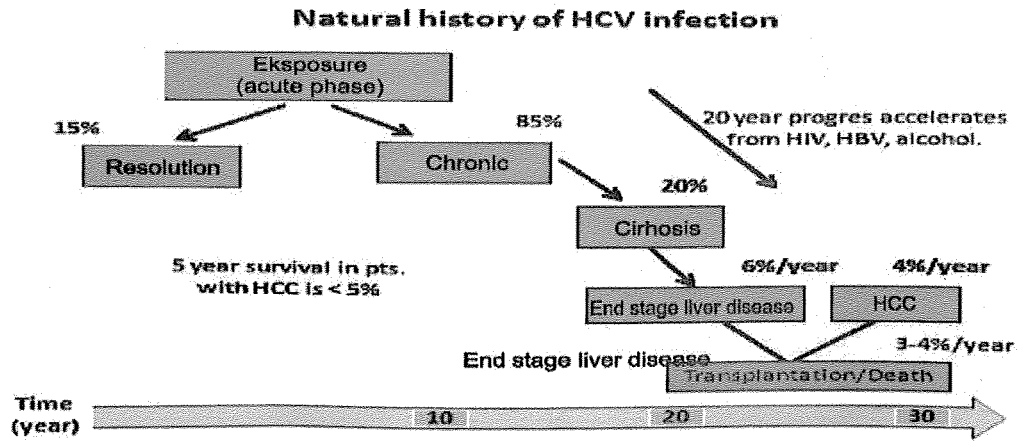
Results: 29 pts terminated the treatment (87.9%, 17 pts in group 1 and 12 in group 2). Negativisation of HCV RNA in weeks 4, 12, 48 and 72 was 42.4 %, 75.7%, 82.7% and 58.6% of pts, respectively (9/17, 52.9% in group 1 and 8/12, 66.7% in group 2). The treatment was discontinued in 4 pts in weeks 6 (1 pt. intersticial pneumonia) and 24 (3 pts, severe trombocytopenia, ascitic decompensation, depression). In these pts HCV RNA was negative in week 12. Side effects of treatment in week 48 were minimal in 8 pts.

Conclusions: Early beginning of standard treatment in pts with chronical hepatitis C, 1b (regardless of the level of ALT) is the most important condition for sustained virological response on the end of it.

Introduction

Genotype 1b of hepatitis C virus (HCV) is the most frequent genotype of virus C. Studies conducted in the U.S. have shown that genotype 1 was found in 74% of cases with chronic infections C in the population of this country. Other genotypes 2 and 3 were found in 22%, while those 4,5 and 6 only in 4% (1,2). In Europe is more or less the same situation (3,4,5). Global prevalence of HCV infection is estimated at about 3% of the total population, with over 170 million carriers of the virus all round the world. About 80-85% of people infected with hepatitis C develop chronic infections. Cirrhosis occurs in approximately 10-20% of people with chronic infection, and HCC in 1-5% of them for a period of 20 to 30 years. The mechanism by which HCV makes liver cancer is still unknown. On the other hand, hepatitis C increases the gravity of the disease when the patient has concomitant other hepatic injuries, especially alcohol (6). The improvements of health care for blood transfusions, medical conditions, etc., today, the main road of virus C transmission in Europe are intravenous drug users and immigrants (7,8).

Figure nr.1 Natural history of HCV infection



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Study

Our study was part of a large European research study known PANTERA ML 21634, representing the center nr. 141318. This study was approved in advance by the Committee of Ethics in dt. March 11, 2008.

The aim of the study was to evaluate the combined treatment with PEGASYS interferon alfa-2a (180μg) and Copegus (ribavirin) to achieve a durable virologic response in patients with increased and normal transaminases (ALT) at the start of treatment.

Patients and methods

We studied 33 patients with chronic hepatitis C, genotype 1b, diagnosed and treated in the Service of Hepatology/Gastroenterology from 2008 to 2010, based on criteria of today guidelines (14). We admitted to the study the patients with chronic hepatitis C without other factors of hepatic damage as the association with HBV, use of alcohol or other etiology. 18 of the patients were males and 15 females, mean age 39.2 years. The patients were divided into two groups: a. 19 pts. with increased ALT, (70.05 ± 29.9 U / l) and b. 14 others with normal ALT, (32.4 ± 10.9 U / l). Treatment schedule was: PEGASYS INF alfa-2a 180 μg/week and ribavirin (Copegus) 1000 - 1200 mg/day for 48 weeks. During the treatment, were followed-up regularly the occurrence of side effects and ALT at weeks 0, 4, 12, 24, 36, 48, 72 and HCV RNA at week 0, 4, 12, 48, and 72. Week 72 coincides with the time of 24 weeks after completion of treatment. In the beginning of treatment ALT and HCV RNA were 58.4 ± 58.4 U/l and 4.68 x 10^5 copies / ml, respectively. Sustained virological response was considered the situation in which the HCV RNA remained negative 24 weeks after completion of treatment. The treatment was complete for 29 pts. In 4 (12.1%) treatment was discontinued because of side effects of drugs.

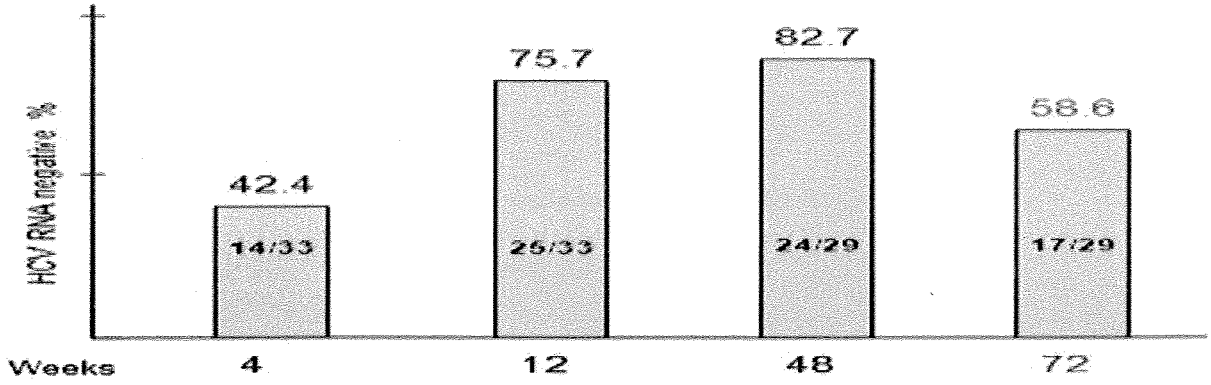
Results

The present studies have established that the most important thing in the treatment with association Pegylated interferon / ribavirin is to follow-up the evolution of HCV RNA over time. Actually, is very known that the low viral load at the beginning of treatment is one of the most important thinks to have a positive result on the end of it. The mean of viral load in our patients was 4.68 x 10^5 copies / ml, which is not a high load. It is for this reason that HCV RNA was negative in 42.4% of patients in the fourth week of treatment, and 75.7 and 82.7, at 12 and 48 weeks, respectively. At week 72 (24 weeks after the treatment), HCV RNA was negative in 58.6% of patients. These data are presented in Table nr.1 and Figure nr.1.

Table nr. 1 HCV RNA during the treatment

Weeks of treatment	4	12	48	72
HCV RNA negative %	42.4	75.7	82.7	58.6

Graphic nr.1. HCV RNA during the treatment



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Week 48: HCV RNA was negative (stable virological response) in 24/29 cases (82.7%) and positive in 5/29 others (17.3%). In 4 of them, ALT was increased at the beginning of treatment. Week 72: HCV RNA was negative (sustained virological response) in 17/29 cases (58.6%). In our point of view, is very important to judge the final results of the treatment, regarding from the preliminary division of the patients in two groups with increase or normal ALT at the beginning of it (Table nr. 2).

So 9/17 (52.9%) of patients with increased levels of transaminases at the start of the treatment made sustainable virological response 24 weeks after the end of it, while in the group with normal ALT at the beginning of it the sustained virological response occurred in 11/12 pts. or 66.7%. We think, that this difference between the two groups was very important (52.9 versus 66.7%) and testifies to the fact how important is the early beginning of the treatment to these patients.

HCV RNA negative at weeks 48 and 72 according to ALT in the beginning of treatment

Nr	ALT \ Weeks	week 48	week 72
17	High ALT	13 (76.4%)	9 (52,9%)
12	Normal ALT	11 (91.6%)	8 (66.7%)

In 4/33 patients some major side effects appeared during the treatment, which led to his suspension. In one patient an interstitial pneumonia was diagnosed in the 6th week of the treatment and after resolution of it he refused to continue, independently of good situation. In three others the treatment was discontinued in 24th week, due to severe thrombocytopenia, ascitic decompensation and depression, respectively. In all three patients HCV RNA was negative at the 12th week. At week 48, 21/29 other patients (72.4%) who completed the treatment had not any side effects. In 8 others the minor side effects were well controlled with symptomatic treatment.

Discussion

The purpose of today's treatment is eradication of HCV (9). According to the guidelines known, all the patients with HCV infection with compensated hepatic disease and who have not contraindications for combined treatment Pegasys INF / ribavirin should be treated, regardless of basalt level of ALT(9). In this logic was supported our study to prove the importance of early treatment in the results of the end of it.

In clinical studies, in which was based the treatment with Pegylated Interferon and ribavirin, virological response (SVR) was achieved in 46% and 42% of patients infected with HCV genotype 1, treated with Pegylated Interferon alfa 2a or Pegylated INF alpha 2b, respectively (10,11,12). It is well documented that sustained virological responses were slightly higher in Europe than in the U.S.A. These studies were confirmed by IDEAL study, which dealt with the comparison of two methods of treatment, approved in the U.S.A. Stable virological response was found 41% with Pegilated INF alpha-2a 180 μg / week plus ribavirin 1.0-1.2 g / day, versus 40% with Pegilated INF alpha-2b 1.5 μg / kg / week plus ribavirin, 0.8-1.4 g / day for 48 weeks (ns) (13). As a strong predictor for a stable virological response were the previously identified genetic polymorphism on chromosome 19, which is adjacent to the region encoding IL28B (or k3 IFN), HCV genotype and the stage of fibrosis. Other predictors of response summarize the basalt level of HCV RNA, the dosage and duration of treatment, the patient factors such as body mass index, age, insulin resistance, gender and hepatic disease characteristics, such as level of ALT, GGT, and stage of fibrosis or coinfections with other hepatotrope virus or with HIV virus (12,14,15,16,17). Even in our study was proved that the level of ALT at the beginning of treatment is very importamt for the final outcome of it. As mentioned above, HCV RNA remained negative 24 weeks after the end of treatment in 66.7% of patients who had normal ALT at the beginning of it, versus 52.9% of those with abnormal levels of ALT. This has a great importance to patients with genotype 1b (which is also the most frequent genotype and most difficult to treat), because the early treatment is the most important condition for a positive outcome on the end. According to current data, the most important thing in the treatment of patients with chronic hepatitis C is to follow-up the viral kinetics during the treatment.

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Is recommended to examine the level of HCV RNA before treatment and at weeks 4,12,24, at the end of treatment and 24 weeks after its completion. If HCV RNA would be negative at fourth week of treatment, (rapid virological response) the duration of treatment would be 24 weeks. If HCV RNA would be negative in 12 week of treatment (early virological response (EVR), the duration of treatment would be 48 weeks. If HCV RNA would be negative in 24 week of treatment (slow virological response), the treatment will continue to 72 weeks.

This has led to the better follow-up of the patients and to achieve a positive effect up to 55% of cases with genotype 1b. This idea is also confirmed by our modest study, although the limited number of cases. On the other hand, if HCV RNA would not be negative at week 24, the possibilities to obtain a sustained virological result response are minimal and retreatments have proven that a positive would be reached only in 4-14% (9).

Conclusions

1. Early Treatment of patients with chronic hepatitis C, genotype 1b, is an important condition to achieve durable virological response at the end of it.
2. Sustained virological response 24 weeks after the end of the treatment, was achieved in 52.9 and 66.7% of patients, with increased and normal ALT at the beginning of it, respectively

References

1. **Alter et al.** Prevalence of Hepatitis C Virus Infection in the United States N Engl J Med 1999; 341:2093-2095.
2. **Blatt et al.** Assessment of hepatitis C virus RNA and genotype from 6807 patients with chronic hepatitis C in the United States. *J Viral Hepatitis.* 2000. Vol. 7,.196–202.
3. **Geoffrey Dusheiko, Hemda Schmilovitz-Weiss et al.** Hepatitis C virus genotypes: An investigation of type-specific differences in geographic origin and disease. Hepatology 1994,Vol.19, Issue 1,13–18.
4. **Francesc X. Lopez- Labrador, Sergj Ampurdanes, Xavier Forns et al.** Hepatitis C virus (HCV) genotypes in Spanish patients with HCV infection: relationship between HCV genotype 1b, cirrhosis and hepatocellular carcinoma. Journal of Hepatology 1997, Vol. 27, 959-965.
5. **Trepo C, Pradat P.** Hepatitis C virus infection in Western Europe. Journal of Hepatology 1999, Vol. 31, 80-83.
6. WHO. Hepatitis C. Fact sheet no. 164.
7. **Juan I. Esteban, Silvia Sauleda, Josep Quer.** The changing epidemiology of hepatitis C virus infection in Europe. Journal of Hepatology 2008, Vol. 48, 148-162.
8. **Adrian M. Di Bisceglie.** Natural history of hepatitis C: Its impact on clinical management. Hepatology 2000, Volume 31, Issue 4, 1014–1018.
9. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. Journal of Hepatology 2011 vol. 55, 245–264.
10. **Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, et al.** Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. New Engl J Med 2002;347:975–982.
11. **Hadziyannis SJ, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, et al.** Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C – a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–355.
12. **Manns MP, Wedemeyer H, Cornberg M.** Treating viral hepatitis C: efûcacy, side effects, and complications. Gut 2006;55:1350–1359.
13. **McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al.** Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. New Engl J Med 2009; 361:580–593.
14. **Marc G. Ghany,Doris B. Strader, David L.** Thomas, and Leonard B. Seeff. Diagnosis, Management, and Treatment of Hepatitis C: An Update. HEPATOLOGY, April 2009, 1355-1374.
15. **Marc G. Ghany, David R. Nelson, Doris B. Strader, David L. Thomas and Leonard B. Seef.** An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases. HEPATOLOGY, October 2011, 1433-1444
16. **Strader DB, Wright T, Thomas DL, Seef LB:** American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. Hepatology. 2004, 39 (4): 1147-1171.
17. **Jason Grebely, Gail V. Matthews & Gregory J. Dore.** Treatment of acute HCV infection. Nature Reviews Gastroenterology and Hepatology 2011, 8, 265-274.