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The use of peginterferon in monotherapy or in combination with ribavirin for the treatment of acute hepatitis C

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Abstract. – BACKGROUND, Acute hepatitis C becomes chronic in 50% of cases. Early treatment seems to be effective in eradicating HCV infection, although no clear recommendations are available in terms of time of initiation, regimen and duration of therapy. We report a retrospective review of 48 patients with acute HCV infection between January 2006 and December 2007.

PATIENTS AND METHODS, This multicenter retrospective study involved three Infectious Disease Units in Sicily and was carried out in three stages: (1) Collection of patients data; (2) Selection of patients according to: elevated ALT (at least 5 times above normal values), seroconversion from negative to positive anti-HCV status; (3) Final selection of patients with a minimum of 12 months follow-up.

RESULTS, Out of 60 patients with a diagnosis of acute HCV infection, 48 were eligible for the study. In 13 subjects (52%) of the 25 who were not treated, the disease resolved spontaneously. 23 patients received pegylated interferon in monotherapy or in combination with ribavirin. 95% achieved a sustained virological response (SVR). Of the 22 sustained responders, 17 (70%) negativized HCV RNA within 8 weeks. No difference appeared between patients receiving monotherapy and those treated with combination therapy. Also, no difference was observed, in terms of SVR, between the two different pegylated interferons given for treatment.

CONCLUSIONS, The rate of viral clearance was higher in the treated group versus the untreated one (95% versus 52%). The SVR found in our study population (95%) was comparable to that reported in other studies. The combination with ribavirin did not appear to impact our sustained response rate, although ribavirin appeared to induce a faster normalization of ALT levels.

Key Words:
Acute Hepatitis C, HCV, Peginterferon, Ribavirin

Introduction

Hepatitis C virus infection is the most common cause of cirrhosis and hepatocellular carcinoma in western countries[1-3]. In Southern Italy the prevalence of chronic hepatitis C is one of the highest in the world[1]). Most cases of HCV infection in this area are related to non-apparent parenteral exposure, intravenous drug use or medical and cosmetic procedures[2,3].

Acute hepatitis C is characterized by a wide spectrum of clinical features ranging from asymptomatic infection to icteric illness[3] and the rate of chronicization is around 50%[4-8].

Although there are no large randomized controlled studies, early treatment of acute hepatitis C appears effective to eradicate infection and to prevent progression towards chronic disease. In comparison with chronic disease, interferon therapy of acute hepatitis seems to be well tolerated with very few drop-outs[9-19]. Howerer, there is no clear recommendation on when to start and which regimen to use. It has been reported that symptomatic individuals have higher probability of eradicating the infection spontaneously[16]. Two german studies have concluded that waiting for as long as 12 weeks before treating did not reduce a sustained virological response (SVR) and that it could be a safe approach especially in symptomatic individuals[16].

As for the duration of therapy, 24 weeks seemed to be more effective: in particular, a 24 week course of either pegylated or standard interferon appears to eradicate HCV infection effectively in 89-94% of those patients who do not experience the spontaneous clearance of the virus[9-11,16]. Twelve weeks should be taken into consideration for genotype 2, genotype 3 and for genotype 1 with a rapid virological response at week 4[16].

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The treatment regimen to use has not been standardized as well, in fact there are no randomized trials or comparative studies between the standards interferons and the new pegylated and between Peg-IFN alpha2a and alpha2b[16]. Finally, a number of studies have hypothesized that the coadministration of ribavirin does not contribute to raise SVR[12-14]. Nevertheless, at the present, no clear guidelines or recommendations concerning the management of patient with acute hepatitis C have been proposed.

Here we report a multicenter retrospective study on 48 patients who were diagnosed to be affected with acute hepatitis C between January 2006 and December 2007, and treated with pegylated interferon monotherapy or in combination with ribavirin.

Patients and Methods

A multi-center retrospective trial was started in January 2009 involving three units of Infectious Diseases in Sicily: The Institute of Infectious Diseases, University of Catania (Hospital Garibaldi), the Unit of Infectious Diseases, Ferrarotto Hospital, Catania and the Unit of Infectious Disaeses, S. Antonio Hospital, Trapani. The first two centers are located in eastern Sicily, whereas the latter is situated in western Sicily.

The study was carried out in three stages.

Firstly, epidemiological, clinical, biochemical and virological data were collected from the clinical records of all patients admitted with a diagnosis of acute hepatitis C between January 2006 and December 2007, either in the ward or in the outpatients clinic.

Secondly, patient cases were selected for the study only when satisfying all three following criteria:

1. High ALT levels (at least 5 times over the upper normal limits);
2. Seroconversion from negative to positive anti HCV antibody as assessed by third generation enzyme immuno-assay, or, as an alternative, conversion to serum HCV RNA positivity, assessed by a qualitative polymerase chain reaction Cobas Amplicor Hepatitis C Virus Test, version 2.0 (Roche Molecular Systems, Branchburg, NJ, USA);
3. Exclusion of any other possible cause of acute hepatic necrosis (drugs, autoimmunity, HAV, HBV, Wilson's disease, Epstein Barr virus and Cytomegalovirus).

Thirdly, only those patients with a minimum follow-up period of 12 months after the onset of the disease were selected and analyzed.

Students' *t* test was used for statistical comparisons.

Results

Sixty patients were admitted to the three hospitals with a diagnosis of acute hepatitis C between January 2006 and December 2007, only 48 were considered eligible for inclusion in the study.

Twenty-five patients received no treatment: 6 because of patients' refusal, 10 because of clear contraindication to interferon therapy, and 9 due to the rapid normalization of ALT levels and spontaneous virological clearance within 12 weeks from the onset of acute disease.

Of the 25 patients who did not receive any therapy, 13 (52%) experienced the spontaneous biochemical and virological resolution of the disease within 12 months after the onset of acute disease, 12 (48%) developed chronic liver disease, as assessed by persistent hyper-ALT and positive HCV-RNA in serum throughout the12 months' follow up. All 12 chronicized cases underwent liver biopsy, which confirmed the chronic disease: 4 cases had a mild chronic hepatitis and 8 had a moderate-severe chronic liver disease with evidence of piecemeal necrosis. In particular, five cases had a fibrosis score ≥ F2 (Metavir score), whereas 7 cases had a fibrosis score < F2.

Twenty-three patients started pegylated interferon 13.6±2 weeks following the onset of acute disease, for 24 weeks; 10 as monotherapy, and 13 in combination with 1000 mg ribavirin daily. Pegylated interferon alpha-2b (1.5 mcg/kg/week) was administered in 14 cases, pegylated IFN alpha-2a (180 mcg/week) in the remaining 9 cases.

A comparison of the epidemiological, clinical and virological parameters of treated and untreated patients at presentation are reported in Table I. A comparison of baseline characteristics between patients who received monotherapy versus those who were treated with combination therapy are reported in Table II.

All subject were followed-up monthly for clinical, biochemical and virological parameters. Treatment response was defined on the basis of normal ALT levels and negative HCV RNA, either at the end of therapy (EOT), or after 6 months of post-treatment follow-up (sustained viral response, SVR).

Of the 23 cases who underwent interferon therapy, 22 (95%) achieved a SVR with ALT normalization. No cases of treatment interruption or dose modification due to side effects were reported.

The only patient who did not respond to therapy was a 44 year-old male who had previously undergone odonthoiatric procedure. He received Peg-IFN alpha-2a plus ribavirin and encountered a mild decrease in ALT levels with no modification of serum HCV-RNA.

Of the 22 sustained responders, 17 (70%) normalized ALT levels and negativized HCV-RNA as soon as 8 weeks after the start of treatment. As shown in Table III, no difference was observed in terms of sustained response rate between patients receiving combination therapy and those treated with pegylated interferon alone.

Actually, only time to HCV RNA negativization resulted significantly ($p = 0.05$) lower in the group of patients treated with combination therapy.

In addition no difference was observed in terms of sustained response rate between 40 kDa and 12 kDa pegylated interferons.

Discussion

The aim of the study was to evaluate the impact of early treatment with pegylated-IFN on the chronicization rate of acute hepatitis C and secondly to compare Peg-IFN monotherapy to Peg-IFN and ribavirin combination. The rate of spontaneous resolution of acute hepatitis in untreated patients was 52% in the control group, this being very high compared to other studies such as those conducted by Santantonio et al[10] and Kamal et al[12] who reported spontaneous clearance rates of 39% and 29.6%, respectively. Nevertheless, in the study carried out by Kamal et al[12], the majority of patients with spontaneous resolution were reported as being of young age, asymptomatic, and non-1 genotype. In our case load, the group of patients with self-limiting disease had no common characteristics in terms of age, risk factors, clinical presentation or genotype.

As expected the rate of viral clearance was higher in the treated group compared with the untreated one (93% vs 52%). This result is comparable with previous data reported in the literature. In 2001, Jaeckel et al[9] reported a high rate (98%) of HCV eradication in patients with acute hepatitis using a six months treatment with IFN alpha2-b. This first randomized study was followed by several investigations that showed, as reviewed by a meta-analysis conducted by Licata et al[15], the benefit of treatment for those acute hepatitis patients who failed to show early signs of spontaneous viral eradication. In 2005 Santantonio et al[10] showed a 94% SVR rate in a cohort of 28 patients. One of the largest study in the field was the HEP-NET Acute-HCV-study conducted by Weiggand et al[11], which involved 53 German centers. This study confirmed the efficacy of Peg-

Table I. Patients' characteristics at baseline between treated and untreated.

	Treated	Untreated
Age	40.5 ± 8	44.5 ± 9
M/F	15/8	15/10
HCV RNA IU	$6.9 \pm 2 \times 10^5$	$7.2 \pm 2 \times 10^5$
ALT IU	599 ± 370	611 ± 407
Genotype 1/2/3	7/6/10	7/6/12
Asymptomatic	10	12
Risk factors		
Drug use	10	12
Surgery	2	2
Tattoo/piercing	2	2
Sex	2	2
Undetermined	7	7

Table II. Baseline characteristics of acute hepatitis C patients who received therapy.

	PEG-IFN n. 10	PEG-IFN + RBV n. 13
Age	39.5 ± 8	41.2 ± 7
M/F	7/3	8/5
HCV RNA IU	$6.8 \pm 2 \times 10^5$	$7.1 \pm 2 \times 10^5$
ALT IU	588 ± 330	611 ± 366
Genotype 1/2/3	3/3/4	4/3/6
Asymptomatic	4	6
Risk factors		
Drug use	4	6
Surgery	1	1
Tattoo/piercing	1	1
Sex	1	1
Undetermined	3	4
Time from clinical onset to therapy (wks)	12.1 ± 1	12.2 ± 1

Table III. Efficacy of PEG-IFN treatment in acute hepatitis C either alone or combined with ribavirin.

	PEG-IFN	PEG-IFN + RBV
EOT (%)	100	92.3
SVR (%)	100	92.3
Time to ALT normalization (wks)	9.9 ± 2.1	6.6 ± 1.4
Time to RNA negativization (wks)	8.9 ± 1.7	5.6 ± 1.2*

*$p = 0.05$ vs. PEG-Interferon alone (Student's t test).

IFN treatment (94% EOT and 89% SVR) but also the importance of patients' selection and monitoring in order to limit the number of drop-outs.

The SVR found in our population (95%) was comparable to that observed in other trials using pegylated interferons[16,17]. The combination of ribavirin did not seem to impact the SVR rate although ribavirin did appear to induce the swifter negativization of HCV RNA in comparison with Peg-interferon monotherapy.

Other studies have also noted the limited benefit of adding ribavirin to the treatment of acute HCV[16]. Rocca et al[14] showed that the addition of ribavirin to standard interferon was not a determining factor in determining the overall response to treatment. Kamal et al[12] concluded that SVR does not change significantly when PEG-IFN is combined with ribavirin (80% vs 85% Peg-IFN monotherapy).

Currently, in the absence of clear large randomized clinical trials, there are no evident recommendations regarding the treatment of patients with acute HCV infection. Not only the type of IFN or Peg-INF to be used, but also the duration of therapy remains to be established. As for the addition of ribavirin, further investigations are certainly needed.

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