Original Article

# Clinical Characteristics, Spontaneous Clearance and Treatment Outcome of Acute Hepatitis C: A Single Tertiary Center Experience

Melanie Deutsch, Nikolaos Papadopoulos, Emilia S. Hadziyannis, John Koskinas

2nd Department of Internal Medicine, Athens University Medical School, Hippokration General Hospital of Athens, Greece

**Address for correspondence:**
Dr. Nikolaos Papadopoulos, 2nd Department of Internal Medicine, Athens University Medical School, Hippokration General Hospital of Athens, 114 Vas. Sophias Ave., 115 27 Athens, Greece.
E-mail: nipapamed@gmail.com

## ABSTRACT

**Background and Aims:** Acute hepatitis C is rarely diagnosed due to its predominantly asymptomatic course. However, early treatment results in viral eradication in a high number of patients thus, preventing chronicity. The aim of our study was to describe our experience with patients with acute hepatitis C virus (HCV) infection who presented and followed-up in our liver unit, pointing on treatment strategy, and outcome. **Patients and Methods:** Retrospective, descriptive study of 30 patients with acute HCV infection (26 males and 4 females) with a mean age of 32 years. **Results:** The source of infection was mainly injection drug use in 17/30 (56.7) and medical procedures 6/30 (20%). Twenty patients (66.6%) were symptomatic. HCV-ribonucleic acid (RNA) was detectable at presentation in 26 (86.7%) patients. The genotype distribution was: 13/26 (50%) genotype 1, 3/26 (11.5%) genotype 2, 8/26 (30.8%) genotype 3 and 2/26 (7.7%) genotype 4. Totally, 9 patients (30%) experienced spontaneous viral eradication. No significant differences could be documented between patients who spontaneously cleared the virus and those who had viral persistence. Thirteen patients (44%) were treated with peginterferon-based regimen. All patients (100%) achieved non-detectable HCV-RNA and had normal serum alanine aminotransferase levels at the end of the treatment. Eleven patients achieved sustained virologic response (SVR), one relapsed and one was lost to follow-up. The overall SVR rate was 84.6%. None of the patients required dose reduction or stopped the treatment due to side effects. **Conclusion:** In conclusion, early initiation of anti-viral treatment in patients with acute hepatitis C results in high-SVR rates (independently of genotype) and is well-tolerated.

**Key Words:** Acute hepatitis, chronic hepatitis, hepatitis C virus

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Infection with the hepatitis C virus (HCV) can result in both acute and chronic hepatitis. The acute phase of hepatitis C is generally defined as the first 6 months of the infection but, overall, approximately 70-80% of the infected individuals will develop chronic infection while only 20-30% will clear the virus spontaneously.[1] The diagnosis of acute hepatitis C is made by testing for anti-HCV and HCV-ribonucleic acid (RNA). Serum HCV-RNA becomes detectable within 2 weeks while anti-HCV antibodies are found positive within 8 weeks of exposure. However, more than 70% of the acutely infected patients are asymptomatic or have a clinically mild course of the disease.[2-4] As a consequence, the diagnosis of acute HCV infection is infrequently made resulting in a limited experience in managing patients with this disease. On the other hand, experience with interferon based therapy showed that, if acute HCV infection is diagnosed early and treated, viral eradication is possible and progression to chronicity may be prevented in the majority of cases.[5] In general, the goal of therapy for hepatitis C is to achieve a sustained virologic response (SVR), defined as undetectable HCV RNA at least 6 months after cessation of therapy. The results of recent studies performed with a relatively small number of patients receiving peginterferon (PegIFN) revealed that treating patients with acute HCV infection results in an SVR rate of 76-95% clearly much higher than expected to occur during spontaneous viral eradication.[6]

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These results led the American Association for the Study of the Liver to suggest that it is appropriate to consider the use of PegIFN in the treatment of acute hepatitis C.[7] In this context, however, many questions are raised: When is the appropriate time of starting treatment? For how long? Should ribavirin (RBV) be added-based on the model of the classical therapy of chronic hepatitis C? Are there predictive factors for spontaneous viral clearance to avoid unnecessary therapy?

Regarding these "grey zone" controversies we decided to describe our experience with 30 patients with acute HCV infection who presented and were followed-up in our liver unit, especially, pointing on treatment strategy and outcome.

## PATIENTS AND METHODS

This is a retrospective analysis of 30 enrolled Caucasian patients with acute HCV infection who presented to our Department between 1/1/2006 and 30/1/2010. The diagnosis of acute HCV infection was made either by (1) elevated alanine aminotransferase (ALT) (>10 times of the normal value) and documented anti-HCV seroconversion (with laboratory tests obtained within the prior 12 months demonstrating negative HCV antibodies) or (2) documented or probable exposure to HCV (based on the patient's history reporting recent risk-factors for acquiring HCV) followed by elevations in serum ALT to above 10 times the upper limit of normal range, positive HCV antibody test and detection of HCV-RNA in serum.

Patients with HIV infection or other obvious cause of acute liver injury (hepatitis A or B, alcoholic hepatitis or drug induced hepatitis) were excluded from this study. We used the recorded data of each patient for initial history, physical examination, and laboratory blood tests including routine liver tests.

The incubation period was calculated for each patient by the time of the documented or suspected exposure to the seroconversion time. HCV-RNA was documented at the time of presentation and 2 months later. In patients with persistent viremia at 2 months of presentation, treatment was initiated and these patients received PegIFN (either alpha-2a, 180 μg weekly or alpha-2b, 1.5 μg/kg weekly) as monotherapy or in combination with RBV. Treated patients were followed-up monthly until at least 6 months after the end of the treatment. Untreated patients who had negative HCV RNA 2 months after diagnosis were followed for at least 6 months after the acute HCV infection.

SVR was defined by undetectable HCV-RNA (using commercial qualitative polymerase chain reaction (PCR) methods) 6 months after the end of treatment. End of treatment response (ETR) was measured as qualitative HCV-RNA determined by PCR at the time of completion of treatment. Patients with negative HCV-RNA at the end of treatment and positive 6 months later were considered relapse responders (RR) and patients with positive HCV-RNA at the end of treatment were considered non-responders.

### Laboratory methods

Blood chemistry values including liver enzymes ALT, aspartate aminotransferase were determined by commercially available assays. Commercially available enzyme immunoassays were used for detection of anti-HCV. Serum HCV-RNA was detected using a commercially available qualitative PCR assay (Amplicor, Roche Molecular Diagnostic Systems, Branchburg, NJ, USA). HCV genotype was also determined by a commercially available assay (InnoLipa, Innogenetics, Gent, Belgium). Levels of serum HCV-RNA were determined by bDNA (Quantiplex HCV RNA, Chiron Co).

### Statistical analysis

General descriptive methods were used for determination of percentages. Means of continuous variables were compared using Student's two-sample *t*-test. Bivariate analysis of categorical data were analyzed with 2 × 2 P-Pearsons Chi-square. $P$ value < 0.05 was considered significant. The SPSS version 16.0 statistical package was used.

## RESULTS

Between January 2006 and January 2010, 30 patients (26 males

**Table 1: Baseline characteristics of the thirty enrolled patients with acute hepatitis C**

| | |
|---|---|
| Age, years | 32.11±12.54 |
| Gender (males), *n* (%) | 26 (86.6) |
| Route of exposure, *n* (%) | |
| Injection drug use | 17 (56.7) |
| Medical procedure[1] | 6 (20) |
| Household contacts[2] | 3 (10) |
| Unknown | 4 (13.3) |
| Jaundice, *n* (%) | 12 (40) |
| ALT, IU/L | 803.5 (400-3763) |
| HCV-RNA, IU/mL | 73558 (700-22×10$^6$) |
| HCV genotype, *n*/*N* (%) | |
| 1 | 13/26 (50) |
| 2 | 3/26 (11.5) |
| 3 | 8/26 (30.8) |
| 4 | 2/26 (7.7) |
| Incubation period, days | 76.33±54.46 |

Quantitative variables are expressed as mean±SD or median (range), [1]Medical procedures consisted of coronary artery bypass graft (CABG) and Percutaneous transluminal coronary angioplasty (PTCA), [2]Blood-to-blood contact with patient known to have HCV infection, HCV: Hepatitis C virus, ALT: Alanine aminotransferase

and 4 females) met the diagnostic criteria for acute hepatitis C and were included in this study [Table 1]. The mean age at diagnosis was 32.11 ± 12.54 years.

The presumed source of infection was mainly injection drug use (IDU) in 17/30 (56.7%) of the patients. Other 6/30 (20%) patients reported previous medical procedures such as cardiac catheterization, surgery or gynecologic intervention. In 3/30 (10%) sexual contact or other "blood to blood" contact with a known patient with chronic HCV infection was reported, while in 4/30 (13.3%) the source of infection remained unknown even after a detailed history taking. The time of exposure could be determined with certainty in 18/30 (60%) patients. In the remaining seven patients, the time of exposure was approximated according to presentation and patient's best recollection. Overall, the incubation period was estimated as a mean of 76.33 ± 54.46 days duration.

Twenty patients (66.6%) were symptomatic. The most common symptoms were jaundice 12/30 (40%), fatigue (80%), abdominal pain (50%), loss of appetite (50%), and dyspepsia (40%). Laboratory testing at presentation showed median ALT levels of 803.5 IU/L (range: 400-3,763).

In 26 (86.7%) patients HCV-RNA could be measured at presentation with a median HCV-RNA level of $7.3 \times 10^5$ IU/ml (range: 700-22 × $10^6$). The genotype distribution in these patients was: 13/26 (50.0%) genotype 1, 3/26 (11.5%) genotype 2, 8/26 (30.8%) genotype 3 and 2/26 (7.7%) genotype 4. Three out of the four patients with negative HCVRNA at presentation–are assumed to have automatically cleared the virus. In these patients the diagnosis was based on HCV seroconversion and ALT elevation. One patient presented negative HCV-RNA at diagnosis but positive 2 months later. This patient has been treated with PegIFN a-2a for 24 weeks resulting in SVR.

Among the 26 patients with positive HCV-RNA at presentation six patients had negative HCV-RNA after 2 months and remained HCV-RNA-negative till at least12 months of follow-up. Totally, nine patients (30% among the total number of patients and 37.5% among those who had follow-up) presented spontaneous viral eradication. Comparing clinical characteristics of the patients who spontaneously cleared the virus with those who had viral persistence, no significant differences could be documented [Table 2].

Two patients (6.7%) were active drug injection users and were not considered as good candidates for treatment. Six patients (20.0%) were lost to follow-up and did not receive anti-viral treatment.

The remaining 13 patients (44.0%) were treated with PegIFN-based regimen. Nine patients received monotherapy with PegIFN, while four received PegIFN in combination with RBV. We initiated therapy in 10.3 ± 7.1 weeks (mean) after diagnosis. Of the 13 patients treated, all (100%) achieved non-detectable HCV-RNA and had normal serum ALT levels at the ETR. The mean treatment duration time was 22 ± 5.7 weeks. One patient with genotype 3 discontinued treatment by her own after week 5. However, she presented at follow-up visits and had negative HCV-RNA 6 months later presenting SVR. Finally, 11 patients achieved an SVR and only one relapsed (RR). One patient was lost to follow-up and we had no available SVR data. Thus, the overall SVR rate was 84.6% [Table 3]. The patient who relapsed has been treated with PegIFN a2b monotherapy and had genotype 1. Side effects experienced by our patients during treatment were typical of those previously reported for PegIFN therapy and included fever, flu-like symptoms, neutropenia and headache. However, none of the patients in study led to dose reduction or stopped the treatment.

**Table 2: Characteristics of the patients who spontaneously cleared the HCV compared with patients who presented viral persistence**

| | Spontaneus clearance (*N*=9) | Viral persistence (*N*=21) | *P* value |
|---|---|---|---|
| Age, years | 29.9±11.7 | 35.6±14.3 | 0.30 |
| Gender, *n* (%) | | | 0.35 |
| Male | 7/9 (77.7) | 19/21 (90.5) | |
| Female | 2/9 (22.3) | 2/21 (9.5) | |
| Route of exposure, *n* (%) | | | 0.19 |
| Injection drug use | 4/9 (44.4) | 13/21 (61.9) | 0.37 |
| Medical procedure | 1/9 (11.1) | 5/21 (23.8) | |
| Household contacts | 1/9 (11.1) | 2/21 (9.5) | |
| Unknown | 3/9 (33.4) | 1/21 (4.8) | |
| Jaundice, *n*/N (%) | 4/9 (44.4) | 8/21 (38.1) | 0.74 |
| ALT, U/L | 1107.9±1060.4 | 955.6±734.6 | 0.65 |
| HCV-RNA, IU/mL | 4412100± 9831942 | 694214± 2034881 | 0.18 |
| HCV genotype, *n*/*N* (%) | | | 0.38 |
| 1 | 2/9 (22.2) | 11/21 (52.3) | |
| 2 | 0/9 | 3/21 (14.3) | |
| 3 | 3/9 (33.3) | 5/21 (23,8) | |
| 4 | 1/9 (11.1) | 1/21 (4.7) | |
| Not done | 3/9 (33.3) | 1/21 (4.7) | |

Quantitative variables are expressed as mean±SD, ALT: Alanine aminotransferase, HCV: Hepatitis C virus

## DISCUSSION

Management of acute HCV infection is of great interest since it seems to represent a chance to prevent progression to chronic hepatitis C. However, the difficulty in depicting patients with acute HCV infection, due to its usually

**Table 3: Outcomes**

| | |
|---|---|
| General Outcomes, *n* (%) | |
| Spontaneously HCVRNA clereance (among patients with follow-up) | 9/24 (37.5) |
| Contraindication for treatment | 2/30 (6.7) |
| Treated patients | 13/30 (43.3) |
| Lost to follow-up | 6/30 (20) |
| Overall period from diagnosis to treatment, weeks | 10.3±7.1 |
| Therapeutic regimens, *n* (%) | |
| Combination treatment (PegIFN+RBV) | 4/13 (30.7) |
| Monotherapy (PegIFN) | 9/13 (69.3) |
| Treatment outcomes, *n* (%) | |
| ETR | 13/13 (100) |
| Overall SVR | 11/13 (84.6) |
| Genotype 1 | 3/5 (60) |
| Genotype 2 | 3/3 (100) |
| Genotype 3 | 5/5 (100) |
| RR | 1/13 (7.7) |
| Lost to follow-up, *n* (%) | 1/13 (7.7) |
| Treatment duration, weeks | 22±5.7 |

Quantitative variables are expressed as mean±SD, PegIFN: Peginterferon, ETR: End of treatment response, SVR: Sustained virologic response, RR: Relapse responders

asymptomatic course, clearly limits this goal.[3,8] Moreover, the exact case definition of recently aquired HCV infection has not been standardized until now with the most studies using a great heterogeneity of diagnostic criteria.[9] Better knowledge of transmission route and better follow-up of "high risk" patients may improve the diagnostic range. It is well known that in Western world the major risk factor for acquisition of HCV infection is IDU. Indeed, almost 60% of the patients in our study were drug users being the most representative cases of acute hepatitis C. Some of these patients were asymptomatic but were routinely examined for anti HCV antibodies by their general physicians who were aware of the risk of infection. In patients who are not in "high-risk" groups for transmission of HCV, diagnosis of acute HCV infection is even more difficult. Interestingly in 20% of our patients iatrogenic transmission of HCV infection could be clearly demonstrated. Although a similar percentage is reported by other studies, the risk of HCV infection during medical procedures is of special concern.[5]

Ten out of the 30 patients were asymptomatic at presentation. The clinical symptoms of the rest of the patients did not differ from the usual symptoms occurring in very acute hepatitis with 12/30 (40.0%) of them presenting with jaundice. On the other hand, the ALT levels at presentation were higher than the levels reported in other studies in patients with acute hepatitis C.[6]

Thirty percent of the patients spontaneously cleared the virus. This percentage is relatively high but is in accordance to the previous reports. Comparing clinical and laboratory characteristics of the patients with spontaneous viral clearance with those who presented viral persistence we couldn't identify possible predictive parameters associated with spontaneous viral eradication. However, these data may be biased because of the small number of patients. Some difference in mean age (29.9 vs. 35.6) with younger patients possibly clearing the virus easily could be observed, but this difference was not statistically significant. Generally, there is some evidence that the development of chronic infection may be lower in patients presenting with symptomatic acute HCV infection reflecting a robust antiviral cellular immunity.[7,10] This could not be confirmed in our study. The role of CD4+ and CD8+ T-cell activation which develops 8-12 weeks after infection is considered crucial in spontaneous resolution. Thus, delaying the treatment in order to give the opportunity to patients to spontaneously clear HCV is a very logical approach.[9,11]

The most important predictive factor for spontaneous clearance in acute HCV infection has been described recently to be related with host factors, especially, with polymorphisms of a site close to the IL28B gene on chromosome 19.[12] These polymorphisms have not been studied in our patients.

One of our patients with clearly evident acute hepatitis C demonstrated by HCV seroconversion had moderate elevated ALT at presentation and undetectable serum HCV-RNA by a sensitive PCR assay. Two months later, he presented with a further elevation of ALT and high viraemia. We believe that this patient's clinical course proves the fact that in acute hepatitis C the HCV-RNA levels may be fluctuating and that more than one viral load measurements must be performed to clarify the real patients' status. There are some other reports with patients who were considered to spontaneously recover as they had undetectable HCV-RNA levels for a period >12 weeks but were found to be HCV-RNA positive several months later.[13]

With respect to treatment, 13 of our patients were treated with pegylated interferon monotherapy or in combination with RBV for 22 ± 5.7 weeks. We started treatment soon after the confirmation of HCV-RNA positivity in the second measurement performed at 8-10 weeks after diagnosis. This was in accordance with the results of other studies which suggest that a delay of 8-12 weeks is the most appropriate time to initiate treatment. In a meta-analysis of acute hepatitis C, SVR rates and timing of treatment initiation revealed that the highest response rates were seen when treatment was started at 12 weeks of diagnosis.[14] Recently, there are some data about better SVR rates achieved when treatment is started as soon as possible (100% vs. 53% when initiating treatment during the 1st month compared with delaying treatment).[10,13,15] Additionally, another study demonstrated that immediate treatment versus treatment starting 12 weeks

after presentation in patients who remained HCV RNA positive resulted in a SVR rate 78% versus 54% ($P = 0.034$).[16]

In our study, all patients achieved ETR, one patient relapsed and one was lost to follow-up. The overall SVR rate in our treated patients was 84.6%, in accordance with the results of other studies reporting SVR rates as high as 60-100%, and substantially better than those observed in chronic hepatitis C.[6,7,9,10,14] These SVR rates demonstrate that patients treated during acute hepatitis C have a significantly higher resolution of hepatitis C than the spontaneous recovery rate (86.6% vs. 30% in our patients).[7]

In other studies, higher SVR rates in patients infected with genotypes 2, 3 and 4 than in those infected with genotype 1 have been reported.[10] Again, our limited number of patients cannot lead us to confirm this finding. The choice between therapeutic regimens (PegIFN monotherapy vs. PegIFN + RBV) in our patients with acute HCV infection was made randomly. It is still unclear, which regimen is the most appropriate. Earlier and recent reports indicate the superiority of PegIFN + RBV regimen in SVR rates.[12,17] However, a recent meta-analysis suggest that monotherapy with PegIFN may be adequate.[12]

In contrast to other reports, the severity of side-effects of the anti-viral therapy was limited in our study.[13] Actually, none of the patients had a serious adverse reaction and none of them reduced or stopped treatment as a result of a side effect despite the fact that a number of patients were intravenous drug users ex-IVDUs. This applies both to patients on monotherapy and/or on combination therapy. One of our patients stopped treatment due to his own wish after 5 weeks but still achieved SVR. Therefore, regarding the excellent treatment results in this group of patients, history of IVDU or possible side effects of treatment should not be an obstacle to rapid therapeutic intervention.[18,19]

In conclusion, our results indicate that early initiation of a 24-week course of PegIFN or PegIFN plus RBV regimen results in high SVR rates and is well tolerated. Further studies are necessary to clarify the optimal duration of therapy and the optimal treatment regimen.

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