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# Treatment results of our patients with acute viral hepatitis C

## *Akut hepatit C hastalarımızın tedavi sonuçları*

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## ABSTRACT

**Aim:** The diagnosis of acute hepatitis C virus (HCV) infection can be made during follow-up in patients with a generally known risk contact, since it is mostly asymptomatic. The earliest indicator of acute HCV infection is increased HCV-RNA. Anti-HCV seroconversion is also the strongest evidence of acute infection. The risk of becoming chronic is at least 80%. Acute HCV infection should be closely monitored for treatment alternatives due to its high chronicity rate. Spontaneous recovery can be seen after 8-12 weeks in acute viral hepatitis C. For this reason, it is recommended to wait 8-12 weeks to start specific treatment. This study was conducted to evaluate the data of the patients we followed up with the diagnosis of acute HCV in our clinic, to determine the most appropriate time to start treatment in acute viral hepatitis C, and to evaluate the effect of Peg-interferon alfa 2a on acute viral hepatitis C cases.

**Materials and Methods:** The data of patients diagnosed with acute viral hepatitis C in our clinic between 2005 and 2015 were evaluated.

**Results:** Twelve patients with acute viral hepatitis C were followed up in our clinic. Twelve of the cases were male, and the mean age was 38.8 ± 7 (range, 25-50) years. Spontaneous recovery was observed in three of our patients after 8-12 weeks of follow-up (HCV-RNA was negative by PCR, AST-ALT values were normal).

Three months after the diagnosis of acute HCV, nine patients without spontaneous improvement were started on pegylated interferon alfa 2a 180 mcg (1x1/week sc) and were treated for six months. Treatment response was 100% at 6-month and 2-year follow-ups.

**Conclusion:** After the diagnosis of acute HCV infection, 8-12 weeks should be waited for spontaneous viral clearance. If acute viral hepatitis C does not improve in the first three months, it should be evaluated for specific treatment. Pegylated interferon alfa 2a may be considered as an alternative therapy in patients who do not develop spontaneous viral clearance after 8-12 weeks.

**Keywords:** Acute viral hepatitis C, pegylated interferon alpha 2a, spontaneous viral clearance.

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## ÖZ

***Amaç:*** *Akut hepatit C virüs (HCV) enfeksiyonu tanısı, çoğunlukla asemptomatik seyrettiği için genel olarak bilinen bir risk teması olan hastalarda takip sırasında konulabilmektedir. Akut HCV enfeksiyonunun en erken göstergesi artmış HCV-RNA'dır. Anti-HCV serokonversiyonu da akut enfeksiyonun en güçlü kanıtıdır. Kronikleşme riski en az %80'dir. Akut HCV enfeksiyonu, yüksek kronikleşme oranı nedeniyle tedavi alternatifleri açısından yakından izlenmelidir. Akut viral hepatit C'de 8-12 hafta sonra spontan iyileşme görülebilmektedir. Bu nedenle spesifik tedaviye başlamak için 8-12 hafta beklenmesi önerilmektedir. Bu çalışma, kendi kliniğimizde akut HCV tanısı ile takip ettiğimiz hastaların verilerini değerlendirerek akut viral hepatit C'de en uygun tedavi başlama zamanını saptamak ve pegile-interferon (peg-IF) alfa 2a'nın akut viral hepatit C vakaları üzerindeki etkisini değerlendirmek amacıyla yapılmıştır.*

***Gereç ve Yöntem:*** *2005-2015 yılları arasında kliniğimizde akut viral hepatit C tanısı alan hastaların verileri değerlendirildi.*

***Bulgular:*** *Akut viral hepatit C'li 12 hasta kliniğimizde takip edildi. Olguların 12'si de erkek olup, yaş ortalaması 38,8 ± 7 (aralık, 25-50) yıl idi. 8-12 haftalık takip sonrasında üç hastamızda spontan düzelme gözlendi (HCV-RNA PCR ile negatif, AST-ALT değerleri normaldi).*

*Akut HCV tanısından üç ay sonra, spontan düzelme olmayan dokuz hastaya pegile interferon alfa 2a 180 mcg (1x1/hafta sc) başlandı ve altı ay tedavi uygulandı. 6 aylık ve 2 yıllık takiplerinde tedavi yanıtı %100'dü.*

***Sonuç:*** *Akut HCV enfeksiyonunda tanı konulduktan sonra spontan viral temizlenme için 8-12 hafta beklenmelidir. Akut viral hepatit C ilk üç ayda düzelmezse spesifik tedavi açısından değerlendirilmelidir.8-12 hafta sonra spontan viral klirens gelişmeyen hastalarda pegile interferon alfa 2a alternatif tedavide düşünülebilir.*



***Anahtar Sözcükler:*** *Akut viral hepatit C, pegile interferon alfa 2a, spontan viral klirens.*


## INTRODUCTION

The prevalence of chronic hepatitis due to HCV in the world is approximately 3%, whereas in Turkey this rate is approximately 1% (1) .

One of the important features of HCV is its high chronicity development at rates up to 80%. Another feature is the asymptomatic course of the acute infection, so they pass the acute period without being diagnosed. This causes a high rate of chronicity. In the chronic period, the rate of permanent response with treatment is low (2).

Most acute HCV cases are asymptomatic and only 20% have jaundice. Most cases of acute hepatitis C infection are difficult to distinguish from chronic infection due to the anicteric course. In both cases, anti-HCV and HCV-RNA are positive. Therefore, acute HCV can be diagnosed rarely in this period. However, history and previous examinations are important in differential diagnosis (3).

For the diagnosis of acute HCV infection, documentation of anti-HCV seroconversion, HCV-RNA positivity or Anti-HCV positivity with Anti-HCV negativity, ALT elevation, and recent HCV contact history must be present (4).

Treatment is strongly recommended in acute HCV infection due to the high rate of chronicity and the low efficacy of treatment in the chronic period (50%). Pegylated interferon alpha monotherapy is highly effective in the treatment of acute viral hepatitis C and provides a high sustained response.

In acute viral hepatitis C infection, direct-acting antiviral (DAA) drugs can be used besides pegylated interferon alpha. It is recommended to treat Sofosbuvir + Ledipasvir for 8 weeks in those infected with genotypes 1, 4, 5, 6.

For those infected with genotype 1b, it is recommended to be treated with Paritaprevir/ritonavir + Ombitasvir + Dasabuvir for 8 weeks.

In all genotypes, Glecaprevir + Pibrentasvir or Sofosbuvir + Velpatasvir or Sofosbuvir + Velpatasvir + Voxilaprevir can be given for 8 weeks. However, there are no adequate studies showing that treatment with DAA is more effective than pegylated interferons (5-7).

As in our study, we also recommend treatment with pegylated interferon alfa, since it is within the scope of reimbursement in our country, easy to use once a week, and a permanent viral response of up to 100%. For this, it is sufficient to be treated with pegylated interferon alfa for 24 weeks.

Permanent response can occur in 98% of cases with this treatment (8). Spontaneous HCV clearance has been reported in the range of 25-30% in studies. It usually takes place within the first 12 weeks (9, 10).

In this study, we aimed to evaluate the spontaneous clearance development status and the efficacy of interferon therapy by evaluating the 2-year follow-up data of the patients followed up with the diagnosis of acute viral hepatitis C in our clinic between 2005 and 2015. These patients were analyzed for risk factors, genotype determination, end-of-treatment response rates, and sustained response rates.

## MATERIALS and METHODS

Between 2005 and 2015, HBsAg, anti-HBcIgM, anti-HCV, anti-HIV, AST, ALT, total bilirubin and direct bilirubin tests were studied in patients who came to our clinic with complaints of loss of appetite, nausea, fatigue, darkening of urine color and yellowing of the sclera. HCV-RNA was studied quantitatively by PCR (Biomerieux, France) in patients with positive anti-HCV.

A diagnosis of acute HCV was made in those who had documented anti-HCV seroconversion, HCV-RNA positivity with Anti-HCV negativity or Anti-HCV positivity and HCV RNA positivity, ALT elevation and a recent history of HCV contact (4). Patients who were diagnosed with acute viral hepatitis C among patients older than 18 years and younger than 65 years were included in the study. Those younger than 18 years of age, older than 65 years of age, those with autoimmune disease, a history of viral and toxic hepatitis, those with psychiatric diseases and any other additional disease were not included in the study. The patients were followed without treatment for two or three months after the onset of acute symptoms. At the end of this period, Peg-interferon alfa 2a 180 mcg (1x1/week sc) was administered to nine patients with anti-HCV positive, HCV-RNA (PCR) positive and high AST-ALT values for six months. Patients were evaluated for response to treatment by testing anti-HCV, HCV-RNA (PCR), AST and ALT values at 3 and 6 months of treatment and 1 and 2 years after the end of treatment.

## RESULTS

Twelve male patients that 25-50 years (mean 38.8±7), anti-HCV positive, HCV-RNA (PCR) positive and other acute viral hepatitis markers negative (HBsAg, anti-HBc IgM, anti-HAV IgM, anti-HIV) were followed up with the diagnosis of acute viral hepatitis C (Table-1).

In their history, tooth extraction in five patients, endoscopic intervention in four patients, and sexual risk in three patients were found to be risk factors in the last 6 months. In the last six months, three patients with sexual risk and nine patients with a history of endoscopy and tooth extraction had negative anti-HCV tests in their previous tests.

The mean AST level of these patients was 425.8±36 IU/ml, the mean ALT level was 515.4±40 IU/ml, and the mean total bilirubin level was 7.6±1.55 mg/dl, and they had direct bilirubin dominance. Anti-HCV and HCV-RNA (PCR) tests were positive in all patients (Table-1).

HCV-RNA (PCR) values were between 400.000 and 1.200.000 IU/ml. The mean was 699.166,66±270.099,58. Serum albumin, creatinine, blood sugar and TSH levels of the patients were found to be normal.

Patients were followed for spontaneous clearance for two or three months after the onset of acute symptoms. Spontaneous viral clearance developed in three patients (25%) at 3 months, with normal AST-ALT values and negative HCV-RNA (PCR). In the other 9 patients, anti-HCV and HCV-RNA (PCR) were positive and AST-ALT values were high.

Among these nine patients who did not develop spontaneous viral clearance three patients with genotype 1b and HCV-RNA (PCR) >800.000 IU/ml were treated at week 8 and the other six patients were treated at week 12 with peg-interferon alpha 2a 180 mcg (1x1/week, sc) for six months (Table-1). At the end of the third month of treatment, serum AST and ALT values returned to normal in all patients. Serum HCV-RNA (PCR) was negative in six patients at the end of the third month of treatment and in all patients at the end of the sixth month. The end-of-treatment response rate was 100%.

The patients were followed for two years for permanent response. In the first year after the end of treatment, transaminases were normal, HCV-RNA (PCR) negative in all patients, and anti-HCV negative in one patient. No recurrence was observed in the second year. The anti-HCV result of the patient who was negative for anti-HCV a year ago was again negative (Table-1).

**Table-1.** Baseline values and follow-up data of the patients.

| Patient No/ age (M:male) | Possible causes of transmission | | | Baseline ALT-AST-Total bilirubin values | | Anti-HCV/ HCV-RNA (PCR) | | | | | geno type | Baseline HCV-RNA(PCR) (IU/ml) values |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | spontaneous clearance | Treatment start week | ALT/AST (IU/mL) | TB (mg/dL) | 1. month | 3. month | 6 .month | 1st year after treatment | 2nd year after treatment | | |
| 1-25 M | Tooth extraction | - | 12th week | 590-450 | 6.8 | +/+ | +/- | +/- | +/- | +/- | 1b | 400.000 |
| 2-36-M | endoscopy | - | 8th week | 490-362 | 6.6 | +/+ | +/- | +/- | +/- | +/- | 1b | 820.000 |
| 3-40-M | endoscopy | - | 12th week | 550-450 | 6.1 | +/+ | +/- | +/- | +/- | +/- | 3 | 1.200.000 |
| 4-47-M | Tooth extraction | - | 8th week | 520-450 | 8.5 | +/+ | +/+ | +/- | +/- | +/- | 1b | 850.000 |
| 5-40-M | endoscopy | + | | 560-445 | 10.4 | +/+ | +/- | +/- | +/- | +/- | 1b | 540.000 |
| 6-41-M | anti-hcv (+) partner | + | | 530-425 | 9.8 | +/+ | +/- | +/- | +/- | +/- | 3 | 1.000.000 |
| 7-36-M | Tooth extraction | + | | 495-450 | 9.4 | +/+ | +/- | +/- | -/- | -/- | 3 | 940.000 |
| 8-39-M | Tooth extraction | - | 8th week | 520-470 | 5.8 | +/+ | +/+ | +/- | +/- | +/- | 1b | 810.000 |
| 9-33-M | Tooth extraction | - | 12th week | 520-440 | 6.4 | +/+ | +/- | +/- | +/- | +/- | 1b | 510.000 |
| 10-45-M | anti-hcv (+) partner | - | 12th week | 450-375 | 6.7 | +/+ | +/- | +/- | +/- | +/- | 1b | 430.000 |
| 11-50-M | Tooth extraction | - | 12th week | 470-410 | 6.9 | +/+ | +/+ | +/- | +/- | +/- | 1b | 420.000 |
| 12-34-M | anti-hcv (+) partner | - | 12th week | 490-380 | 7.8 | +/+ | +/- | +/- | +/- | +/- | 1b | 470.000 |

Patient no: 5-7: Those who developed spontaneous viral clearance.

Anti-HCV negative patient was genotype 3 and had spontaneous viral clearance.

Two of the three patients with spontaneous recovery had genotype 3 and HCV-RNA (PCR) > 800.000 IU/ml, and the other patient had genotype 1b and HCV-RNA (PCR <800.000 IU/ml).

Peg-interferon alfa 2a treatment was started in nine patients who did not show spontaneous recovery. One of these 9 patients was genotype 3 and HCV-RNA (PCR) was 1.200.000 IU/ml. The other eight patients were genotype 1b, and three of these 8 patients had HCV-RNA (PCR) values >800.000 IU/ml and five patients <800.000 IU/ml. As a result of these values, peg-interferon alpha monotherapy was started in three patients with genotype 1b and HCV-RNA (PCR)> 800.000 IU/ml at week 8, and for other patients at week 12. Three patients with genotype 3 came from Nakhchivan Autonomous Republic. Our response rate was 100% at the end of the treatment and at the long-term 2nd year controls of our patients.

## DISCUSSION

It is difficult to distinguish acute HCV from chronic HCV infection because immunoglobulin-M (IgM) antibodies cannot be detected in the acute phase of HCV infection, anti-HCV IgG positivity cannot be determined, and HCV-RNA is positive in both chronic and acute infections (11).

It is emphasized that patients with acute hepatitis C respond well to IFN alpha therapy and therefore should be treated in the acute phase. Because it becomes chronic at a rate of 80% and the permanent response rate is low in the chronic period (2).

Two pieces of evidence support that treatment can prevent progression to chronic infection. First, anti-retroviral therapy in patients with acquired immunodeficiency allows the patient's immune system to control viral replication by reducing viral load. Latter; Early control of viral load in lymphocytic choriomeningitis virus infection (murine model) prevents the

development of chronic infection by allowing the host's immune system to clear the virüs (2).

The 2002 NIH consensus conference stated that treatment is necessary in acute HCV infection because of high sustained viral response rates (83-100%) (12).

In the study by Jaeckel et al., it was reported that a 98% permanent viral response was achieved with IFN alpha monotherapy in 44 patients with acute HCV (2).

In a meta-analysis, in 1075 cases of acute HCV infection in 22 studies, a sustained viral response rate of 78% in treated patients and 55% in untreated patients was reported (4).

In a study using pegylated interferon alfa to determine the duration of treatment, sustained viral response rates were 67% at 8 weeks, 82% at 12 weeks, and 91% at 24 weeks. At the end of the study, it was stated that a higher rate of permanent viral response would be obtained with 24 weeks of use (13).

American Association for the Study of Liver Disease's (AASLD) 2004 guidelines recommend administration of pegylated interferons for at least 6 months, as they have similar results to standard interferon alfa and are easy to use (14).

In our study, we applied Peg-interferon alfa 2a 180 mcg (1x1/week sc) treatment for six months to patients who did not develop spontaneous clearance, and a 100% permanent viral response was obtained.

In a study by Gerlach JT et al, spontaneous viral clearance developed in 24 (52%) of 46 patients within 12 weeks of symptom onset in patients with symptomatic acute HCV (15).

In a study by Hofer H et al, spontaneous viral clearance developed in 8 (67%) of 12 patients with symptomatic acute HCV (16).

AASLD's 2004 guidelines also recommend waiting for spontaneous recovery and starting treatment in 2-4 months (14).

As a result of the meta-analysis of 12 studies investigating whether treatment delay has a negative effect on persistent viral response; It has been shown that delaying treatment for 60 days after the onset of symptoms does not reduce the effectiveness of treatment (17).

3-month wait strategy for spontaneous viral clearance in patients with symptomatic acute HCV avoids unnecessary treatment in subjects who will be cleared spontaneously (18).

In our study, spontaneous clearance developed in 25% of the patients. Other patients were started on treatment after 8 or 12 weeks of follow-up and the treatment response was 100%.

In a study by Kamal et al with Pegylated interferon alfa, a better sustained viral response rate was found in genotypes 2, 3 and 4 than genotype 1. No difference was found between starting treatment at week 8 or 12 in genotypes 2 and 3.

It has been reported that patients with genotype 1 and high viral load (> 800,000 IU/mL) have higher SVR when treatment is started early (19).

In cases with HCV-RNA positivity; It is recommended to start treatment at week 8 in cases with genotype I and high viral load (> 800,000 IU/ml), and at week 12 in cases with viral load <800,000 IU/ml (9).

In our study, we followed our patients for spontaneous clearance during 8 or 12 weeks of follow-up in accordance with the literature. We started treatment at the eighth week in 3 patients with high viral load and genotype 1b. We continued to follow the other patients until the 12th week and started treatment for those who did not develop clearance.

In studies evaluating the efficacy of pegylated interferons in acute HCV infection, sustained virological response rates vary depending on genotype and viral load when treatment is started at 8 and 12 weeks after the onset of infection.

In a study by Sanaa et al., Pegylated interferon alpha treatment was started in 42 patients at 8 weeks, 41 patients at 12 weeks, and 38 patients at 20 weeks in patients who did not develop spontaneous clearance.

Persistent viral response rate was reported as 95.3% in the group of patients who started treatment at week 8, 93.2% in the group started at week 12, and 76.6% in the group started at week 20. Since the sustained viral response rates were significantly higher than the 20th week, it was reported that the most appropriate time for treatment was the 8th and 12th weeks (9).

In a meta-analysis, 1075 cases with acute HCV infection in 22 studies were evaluated according to the time to start of treatment and the sustained viral response (SVR) achieved, and the rates of SVR were 82.5% for those who started treatment within 12 weeks, and 70% for those who started treatment within 12-24 weeks, 62.5% of those who started treatment after 24 weeks. In this study, the rate of SVR was found to be

significantly higher in the patient group who started treatment at the 12th week (13).

In a control group study conducted by Karnal et al., in 175 patients with acute HCV infection, pegylated interferon alfa was started once a week for 12 weeks in the 8th, 12th and 20th weeks without spontaneous viral clearance within the first 8 weeks after HCV -RNA positivity and at the end of the study. Permanent viral response rates in these weeks were 95%, 92% and 76%, respectively (19).

In our study, the sustained viral response was 100% in patients who started treatment at both week 8 and week 12.

In a study evaluating the efficacy of the combination of pegylated interferon and ribavirin in patients with acute HCV (genotypes 1 and 4), pegylated IFN + ribavirin was used in 20 cases, and pegylated IFN was started at week 12 and given for 24 weeks. Persistent viral response rates were found to be 85% in the IFN+ ribavirin group and 80% in the monotherapy group, and the difference was not statistically significant and ribavirin combination was not recommended (20, 21).

There was no patient who was given ribavirin treatment in the patients included in our study.

The most important limitation of our study is its retrospective nature, the small number of cases and the absence of a control group.

## CONCLUSION

Acute HCV infection is a curable disease with a high rate of permanent viral response when appropriate follow-up and treatment is applied.

In acute HCV infection, since spontaneous viral clearance may occur, treatment should not be started immediately, but should be waited for 8-12 weeks.

Acute viral hepatitis C should be treated with specific therapy if it does not improve in the first 3 months.

It is possible to obtain a 100% permanent viral response with a weekly pegylated interferon alfa treatment.

**Conflict of interest**: The authors declare that they have no conflict of interest.

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