



# Recurrence Rate of Hepatitis C Virus After Achieving a Sustained Virologic Response in Kurdistan Region, Iraq

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## Abstract

**Background:** Hepatitis C virus (HCV) is a public health issue. Successful treatment of HCV infection results in sustained virologic response (SVR) in the majority of subjects. Subsequent recurrence of HCV, either from late relapse or reinfection, may occur. The aim of this study was to assess the recurrence rate of HCV in Iraqi patients.

**Methods:** In this study, 113 patients who completed anti-HCV therapy successfully were recruited. While 23 patients received a classical regimen of peg-interferon plus ribavirin, 90 patients received direct-acting antiviral therapy. Those patients were followed up for three years. HCV recurrence rate was calculated using events/person years of follow-up (PYFU).

**Results:** Among the recruited patients, HCV RT-PCR was positive in 1 (0.88%) patient giving a recurrence rate of 2.95 per 1000 PYFU. When the data were stratified according to the treatment regimen, the recurrence rate was 14.49 per 1000 PYFU in patients who received the classical regimen of interferon and ribavirin.

**Conclusions:** The overall recurrence rate was low in Iraq. No recurrence was recorded in patients received direct-acting antiviral therapy. Further studies are needed with a larger sample size and longer follow-up to determine the relapse rate in Iraq.

**Keywords:** HCV, Sustained virologic response, Recurrence rate

## Background

Infection with hepatitis C virus (HCV) is a public health problem that is associated with deleterious consequences such as liver cirrhosis and hepatocellular carcinoma (1). Recent estimates suggest that more than 150 million people are chronically infected with the virus and over 500 000 subjects die annually of the infection (2). With the approval of direct-acting antivirals for the treatment of HCV, outstanding progress has been made that made the elimination of the virus feasible (3). Successful treatment with the achievement of sustained virologic response (SVR) reduces the risk of complications such as cirrhosis and cancer. One of the challenges to treatment is the risk of late relapse after finishing the treatment. The prevalence of HCV in Iraq has been studied thoroughly and it has been reported to be low in all regions of the country (4-7). The most common HCV genotype in Iraq is genotype 1 followed by genotype 4 (8). Additionally, reports from our country showed a very high SVR rate in patients with hemoglobinopathy and end-stage kidney diseases (9,10). The aim of this study was to investigate the relapse rate of HCV 36 months after the completion of the treatment

## Materials and Methods

### Patients

Annually, invitations were sent to patients who were previously infected with HCV and completed treatment course successfully as defined by negative RT-PCR results 12 weeks after the end of treatment in patients who received direct-acting antiviral therapy. This was performed for 3 years.

### HBsAg and HIV ELISA

Commercial ELISA kit (DIA.PRO Diagnostic Bioprobes ELISA kit, Italy) was utilized to test HBsAg and HIV positivity.

### RNA Extraction

HCV nucleic acid was extracted using QIAamp RNA Extraction Kit (Qiagen) following the manufacturer's instructions for automatic extraction in QIAcube extractor (Qiagen). Then, the purity and concentration of RNA were measured by NanoDrop.

### HCV Quantification and Genotyping

Nucleic acid amplification was conducted using artus HCV RG-RT PCR Kit and was run on a Rotor-Gene

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Q thermocycler. In this procedure, the amplification of HCV RNA ranged from  $65-10^6$  IU/mL for HCV. Then, positive samples were sent for genotype study. The genotyping was carried out using GEN-C 2.0 reverse hybridization strip assay (Nuclear Laser Medicine, Settala, Mi, Italy). In this procedure, the variations in the 5'-UTR and core regions were used to discriminate between HCV genotypes.

### Results

#### Patients

In this study, 113 patients were recruited. While 23 patients received the classical regimen of peg-interferon plus ribavirin, 90 patients received direct-acting antiviral therapy. Among them, 64 (56.63%) were male and 111 (98.23%) were treatment-naïve (patients without prior treatment for HCV) (Table 1). Among these patients, 47 (41.59%) were infected with genotype 1 while 49 (43.36%) were infected with genotype 4 (Table 1). Then, all patients were tested for HBV and HIV. Among them, 1 (0.88%) was HBV positive, whereas all patients were negative for HIV.

#### HCV RT-PCR and Relapse Rate

In this study, HCV recurrence rate was calculated using events/person years of follow-up (PYFU) (11). Patients

were followed up for 3 years. HCV RT-PCR was positive in 1 (0.88%) patient giving a recurrence rate of 2.95 per 1000 PYFU. When the data were stratified according to the treatment regimen, the recurrence rate was 14.49 per 1000 PYFU in patients who received the classical regimen of interferon and ribavirin. The genotype study showed that the patient with relapse was infected with HCV genotype 4. The previous record of the patient showed that he was without co-morbidity and was infected with HCV genotype 4. The patient was treated with the classical regimen of peg-interferon and ribavirin for 48 weeks. The HCV RT-PCR was negative at the end of the treatment (end of treatment response) and HCV RT-PCR was negative 24 weeks after the completion of treatment (sustained virologic response).

### Discussion

Infection with HCV is a common public health issue especially in developing countries such as Iraq. Such an infection is associated with deleterious consequences predisposing to liver cirrhosis and hepatocellular carcinoma. Early diagnosis and treatment of this infection can prevent those complications. The prevalence of HCV has been studied thoroughly in Iraq and it has been reported to be low (5,12). Therefore, the approval of new powerful drugs for the treatment of HCV may help the elimination of the virus in the country. Post-treatment relapse or reinfection represents a challenge to the elimination plan. In this study, the overall recurrence rate was 2.95 per 1000 PYFU. The vast majority of the studies investigating HCV recurrence rate recruited patients who received the classical treatment of interferon plus ribavirin. Hence, to avoid the bias of recruiting patients who received direct-acting antiviral therapy, our data were stratified according to the regimen used in the treatment. In patients who received the classical regimen of interferon and ribavirin, the recurrence rate was 14.49 per 1000 PYFU. The patient with recurrent infection was infected with genotype 4 which is the same genotypes that was infected with before treatment. This suggests relapse rather than reinfection. However, sequence-based phylogeny is needed to distinguish between relapse and intra-subtype reinfection (13). In a previous study conducted in Germany, the post-treatment relapse rate was 3.30 per 1000 PYFU in patients who were treated with interferon and ribavirin. In a study conducted in Korea, the recurrence rate was 45.96 per 1000 PYFU. In another study conducted in Spain recruiting patients who were treated with the classical regimen, the recurrence rate was 2.50 per 1000 PYF. In a meta-analysis study analyzing relapse rate in 43 studies, the patients were classified into two groups of high-risk and low-risk patients. The relapse rate in the low-risk group was 22.23 per 1000 PYFU while it was 1.85 per 1000 PYFU in the high-risk group (11). In the same study, the relapse rate

**Table 1.** Characteristics of Subjects Recruited in the Study

Characteristics	No.	%	
<b>Patients Received DAA*</b>			
Genotype	G1	41	45.56
	G3	8	8.89
	G4	41	45.56
Gender	Male	53	58.89
	Female	37	41.11
Naivety	Yes	88	97.78
	No	2	2.22
Co-morbidity	Thalassemia	11	12.22
	No	79	87.78
<b>Patients Received Interferon Plus Ribavirin</b>			
Genotype	G1	6	26.09
	G3	9	39.13
	G4	8	34.78
Gender	Male	11	47.83
	Female	12	52.17
Naivety	Yes	23	100
	No	0	0.00
Comorbidity	Thalassemia	23	100
	No	0	0.00

\*DAA: direct-acting antiviral.

for patients with HIV/HCV coinfection was 32.02 per 1000 PYFU (11). The differences among these studies are difficult to explain; however, the patient's genetic makeup and virus genotypes can partially explain the differences. The data about the recurrence rate of HCV after receiving potent direct-acting antivirals are sparse. In this study, no recurrence was found in patients who received direct-acting antiviral therapy. Further studies are required with a large sample size and monitoring for longer duration is required to determine the recurrence rate after those medications.

To conclude, the overall recurrence rate was low in Iraq. No recurrence was recorded in patients who received direct-acting antiviral therapy. Further studies are needed with a larger sample size and longer follow-up to determine the relapse rate in Iraq.

#### Conflict of Interests

None.

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#### Ethical Approval

The study protocol was approved by the Research Ethics Committees of the College of Medicine, University of Zakho, Kurdistan Region, Iraq. Informed consent was obtained from all participants.

#### Authors' Contribution

All the authors were involved in designing, conducting, extracting data and writing the manuscript. All authors had primary responsibility for the final content of the manuscript and all authors read and approved the final manuscript.

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