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Editorial

Durability of antiviral therapy for chronic hepatitis C after achieving sustained virological response

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Hepatitis C virus (HCV) causes various liver diseases including acute hepatitis, chronic hepatitis, health-holders, liver cirrhosis and hepatocellular carcinoma.[1] Acute hepatitis C progresses to chronic hepatitis from 75 to 85% and cirrhosis after 20-25 years later. In patients with HCV-positive cirrhosis, the annual incidence of hepatocellular carcinoma has been reported as 5% approximately.[1]

The current standard antiviral treatment with peginterferon and ribavirin combination therapy is effective in about 50% of patients with chronic hepatitis C. It is assumed that achievement of sustained virological response (SVR) after the combination therapy, confirmed by means of commercial HCV RNA detection assays is regarded as a cure for chronic hepatitis C (Table 1). It is associated with histological improvement, reduced the risk of hepatocellular carcinoma and liver related mortality, and improved quality of life.

Table 1. Commercially available HCV RNA detection assays

Assay	Manufacturer	Method	Detection limit or dynamic range (IU/mL)
Qualitative HCV RNA dection assays			
Amplicor™ HCV 2.0	Roche Molecular System	Manual RT-PCR	50
Cobas Amplicor™ HCV 2.0	Roche Molecular System	Semi-automated RT-PCR	50
Versant™ HCV	Siemens Health Care Diagnostics	Semi-automated TMA	10
Quantitative HCV RNA detection assays			
Amplicor™ HCV Monitor	Roche Molecular System	Manual RT-PCR	600-500,000
Cobas Amplicor™ HCV Monitor 2.0	Roche Molecular System	Semi-automated RT-PCR	600-500,000
HCV SuperQuant™	National Genetics Institute	Semi-automated RT-PCR	30-1,470,000
Versant™ HCV RNA 3.0	Siemens Health Care Diagnostics	Semi-automated bDNA signal amplification	615-7,700,000
Cobas TaqMan™ HCV Test	Roche Molecular System	Semi-automated real-time PCR	43-69,000,000
Abbott RealTime™ HCV	Abbott Diagnostics	Semi-automated RT-PCR	12-10,000,000

HCV, hepatitis C virus; RT-PCR, reverse transcription polymerase chain reaction; TMA, transcription-mediated amplification; bDNA, branched DNA.

Keywords: Hepatitis C; Sustained virological response; Durability

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For the respect of the durability of SVR, several studies have been reported. Marcellin et al[2] reported that an SVR after antiviral therapy was associated with long-term biochemical and virological responses as well as histologic improvement. Eighty-patients who had SVR after interferon-alpha monotherapy, mean follow-up of 4 years showed that 96% had undetectable serum HCV RNA. In a large-scale clinical trials, 7 (2%) among 400 sustained virological responder had detectable hepatic HCV RNA during follow-up; 5 have been followed and 2 (0.5%) were reappearance of serum HCV RNA at 12 months after therapy.[3] Many other reports including the study of Choi et al[4] confirmed that late relapse is rare after achievement of an SVR with completion of interferon without or with ribavirin therapy (Table 2).[5-13] On the other hand, earlier reports showed higher rate of late relapse.[14-16] These discrepancies may be resulted from use of HCV polymerase chain reaction (PCR) assays with varying degrees of sensitivity and a range of patient populations. As a result, the true durability of the response remains unclear, and the optimal follow-up for patients who have achieved an SVR is unknown.

Even then achievement of an SVR, there are many evidences that HCV can persist and replicate in peripheral blood mononuclear cells, hepatic tissue and other organs including kidney, heart, pancreas, intestine, adrenal gland, lymph node and gallbladder in spite of still undetectable serum HCV RNA.[3,17-21] It is so called "occult HCV", which can be reservoir of reappearance HCV RNA in serum[3,21] and thus play a role in the persistence and reactivation of infection. Highly sensitive reverse transcription and nested PCR assays detected residual HCV RNA in case of occult HCV. However, these assays are not currently standard diagnostic procedures and whether these findings actually represent a replication-competent virus or have any clinical significance is not clear. The immunologic mechanism of HCV recurrence after SVR is also not well investigated. Quiroga et at[22] reported HCV-specific cellular immune responses are stronger in occult HCV infection than in chronic hepatitis C and it would be the cause of the rare incidence of late relapse.

For the factors affecting the durability of SVR, no distinct pattern of baseline characteristics could be identified. Several studies with small number of patients reported the transfusion, injection drug use or dose reduction as a risk factor. However, it was unknown whether these cases reflect relapse or re-infection because of the paucity of paired samples.

Although there is reappearance of serum HCV RNA in approximate 1% of patients with an SVR, individuals who have achieved an SVR should have a single additional follow-up HCV RNA measurement performed to ensure that the negative HCV RNA result at 6 months posttreatment was not a false negative

Table 2. Reappearance rates of serum HCV RNA after achieving SVR

Authors (published year)	Patients No.	Follow-up period (years)	Detectable serum HCV RNA (%)
Marcellin et al[2] (1997)	80	4.0 (mean)	4
Reichard et al[14] (1999)	26	5.4 (mean)	8
McHutchison et al[3] (2002)	400	0.5 (maximum)	0.5
Veldt et al[5] (2004)	286	4.9 (maximum)	4.7
Khokhar[15] (2004)	57	3.0 (maximum)	8.8
Formann et al[6] (2006)	187	2.4 (median)	0
Desmond et al[7] (2006)	147	2.3 (mean)	0.7
Lindsay et al[8] (2008)	366	4.8 (mean)	1
Maylin et al[9] (2008)	344	3.3 (mean)	0
George et al[10] (2009)	147	5.4 (median)	0
Kim et al[11] (2009)	73	1.8 (maximum)	1.4
Swain et al[12] (2010)	1,343	3.9 (mean)	0.9
Trapero-Marugán et al[13] (2011)	153	6.1 (mean)	0
Lee et al[16] (2011)	68	1.8 (median)	7.4
Choi et al[4] (2011)	224	1.5 (median)	0

HCV, hepatitis C virus; SVR, sustained virological response.

possibly due to faulty sample collection. If the second post-treatment HCV RNA measurement is negative, the SVR appears to be durable and a reliable sign of cure after antiviral therapy in chronic hepatitis C. However, it is recommended to follow up serum HCV RNA for a long time after an SVR for those individuals who show intermittent viral breakthrough during treatment or who may be considered at risk for reinfection or late relapse.

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