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Treatment of Non-cirrhotic Incarcerated Genotype 6 Chronic Hepatitis C Injection Drug Users, Compared with Genotype 1

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Abstract

The experience of treatment for hepatitis C virus genotype 6 (HCV-6) was limited in Taiwan due to rare incidence in general population and lack of medical care in the correction facilities where HCV-6 was endemic. This work was to investigate the response of treating HCV-6 incarcerated injection drug users (IDU), compared with HCV-1 incarcerated IDUs. 106 inmates completed treatment and follow-up (39 HCV-6, 67 HCV-1, cirrhosis or co-infection with hepatitis B virus or human immunodeficiency virus excluded) were enrolled in this retrospective study among 182 registered peginterferon/ribavirin therapies of National Health Insurance (NHI) reimbursement in the Kaohsiung and Pingtung correcting facilities from 2014 to 2017. Among the 67 HCV-1 and 39 HCV-6 patients, there was no difference with regard to patient's demographics, hemogram, baseline HCV viral load, except for a higher alanine aminotransferase (ALT) level in HCV-6 patients than HCV-1 patients. Afterword, a higher rapid viral response (RVR) was noted in HCV-6 (64% vs 41%, p=0.018), the sustained viral response (SVR) in HCV-6 or HCV-1 patients who received at least one dose of treatment and the patients who completed the full course of treatment were comparably excellent, (100% vs 89%, p=0.16) and (100% vs 91%, p=0.19) respectively. Although interferon-free direct acting antiviral agents (DAA) are the mainstay of therapy in the world, the peginterferon/ribavirin may be an alternative option for the incarcerated IDU patients with HCV-1 or HCV-6 infection, based on the excellent SVR rate and the limited governmental support for DAA treatment. (J Intern Med Taiwan 2018; 29: 393-400)

Key Words: Hepatitis C, Incarcerated, Inmates, Jailed, Peginterferon

Introduction

Hepatitis C virus (HCV) infection was a global health problem which leads to severe end stage liver disease.[1] In Taiwan, HCV infection was prevalent around at 4.4% in the general population, and up to 58% in some hyper-endemic areas[2,3]. HCV-1 and HCV-2 account for the majority of HCV infections.[4] In particular, HCV-1b was the dominant genotype --- 58-73% in north Taiwan and 48-64.3% in south Taiwan[3,5-8]. The clinical course of HCV infection was associated with disease progression, especially HCV-1b had higher risk of developing cirrhosis and hepatocellular carcinoma (HCC) than other HCV

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genotypes[9-12], and sustained viral response (SVR) of HCV reduced HCC and improved survival in chronic hepatitis C[13.14].

HCV-6 was predominantly found in countries of south Asia, such as Singapore, Thailand, Vietnam, Myanmar, as well as surrounding countries including south China, Hong Kong, and Macao[15]. The prevalence of HCV-6 was ever reported to be 50% in Vietnam and 31% in North Thailand[16,17]. In Taiwan, HCV-6 was rare in the general population, but not unusual with a prevalence of 28% in injection drug users[15]. The distinct distribution of HCV-6 between the general population and IDU was associated with the travel route of illegal drugs from southeast Asia and south China, where HCV-6 was dominantly found[16-18]. The response of peginterferon/ribavirin to eradicate HCV-6 was reported to be superior to HCV-1, and comparable to HCV-2[19,20]. The longer therapy duration of 48 weeks was also reported to be better than that of 24 weeks[21]. From the Asian and Taiwan experiences for HCV eradication, 24 weeks peg interferon/ribavirin therapy achieved a comparable SVR rate if rapid viral response (RVR) was achieved[22,23]. Therefore, response guided therapy for HCV, regardless of genotype, was reimbursed by Taiwan Bureau of National Health Insurance (NHI). However, the experience of HCV-6 therapy was limited in Taiwan because of its rare prevalence in the general population and the lack of medical services in the hyper-endemic groups of IDUs. The NHI reimbursed expenses of the correctional systems from 2014 onward, so jailed IDUs had the opportunity to receive therapy for chronic hepatitis C, with the SVR rate at around 95% in general, and the distribution of genotype 6 about 31%[24]. This work is to explore the difference of response guided peginterferon/ribavirin regimen to treat HCV-6 and HCV-1 prisoners in south Taiwan.

Materials and methods

Incarcerated HCV patients in two correctional facilities (Kaohsiung and Pintung) underwent peginterferon / ribavirin therapy from 2014 to 2017 were enrolled in this retrospective study, but HCV inmates sentenced less than 18 months, received interferon-based therapy, cirrhosis detected by sonogram, co-human immunodeficiency virus (HIV) / hepatitis B virus (HBV) infection, or with autoimmune disease were excluded for analysis. Response guided peginterferon/ribavirin therapy was administered via the guidelines of the Taiwan Bureau of NHI—peginterferon alfa-2a 180 mcg/week plus weight-based ribavirin (1200 mg/day if body weight (BW) > 75 kg, 1000mg/day if BW < 75 kg) with treatment duration of 24 weeks if rapid viral response (RVR) was achieved and 48 weeks if RVR was not achieved. Peginterferon/ribavirin was discontinued if patient failed to achieve early viral response (EVR). These patients were cared at a regular hepatologist clinic inside the correction facility and these patients received outpatient visits every 4 weeks at a correctional clinic when they stayed on course. HCV viral load was detected routinely at week 4, 12, 24, end of treatment, and at 6 months after treatment. Moreover, general medical care was available in daily general practice clinics inside the facility on weekdays. Erythropoietin and transfusion were not provided if anemia developed, given the side effect of ribavirin.

HCV RNA (Abbott Laboratories. Abbott Park, Illinois, USA, lower limit of quantification [LLOQ: 12 IU/mL]) and HCV genotyping (Abbott RealTime HCV genotype II, Abbott Laboratories. Abbott Park, Illinois, U.S.A) were used for HCV RNA analysis, and RVR was defined as undetectable HCV RNA level at week 4 of treatment. EVR was defined as undetectable HCV RNA level, or at least 2–$\log_{10}$ decrease HCV RNA levels from baseline at week 12 of treatment. End-of-treatment virologic response (EOTVR) was defined as undetectable HCV RNA level at the end of treatment and SVR was defined as undetectable HCV RNA level 6 months after the

end of treatment.

The study outcome would be only the comparison of SVR between patients with HCV-6 and HCV-1 infection. Results were expressed as the mean (standard deviation) for quantitative variables and frequency for categorical variables. Normally distributed quantitative variables were analyzed by Student's t-test, and categorical variables with the chi-squared test.

Results

Of the 182 HCV inmates in Kaohsiung and Pingtung correctional facilities receiving pegainterferon /ribavirin between March 2014 and December 2017, 54 (29.6%), 44 (24.1%), 45 (24.7%), 20 (11%), 14 (7.7%) and 5 (2.7%) had HCV-1a, HCV-1b, HCV-6, HCV-2, HCV-3 and mixed genotype infection. Thirty-nine (21.4%) patients were excluded from the study because of HCV-2, HCV-3 or mixed genotype infection. Of the remaining 143 HCV-1 or HCV-6 patients, 37 patients were excluded because they were still on treatment or received post-treatment follow-up < 6 months. The remaining 106 patients (HCV-1 and HCV-6 in 67 and 39 patients, respectively) with confirmed outcome were enrolled in the study. Five (4.7%) patients prematurely discontinued treatment due to treatment-emergent adverse events (including hyperthyroidism, psoriasis, and

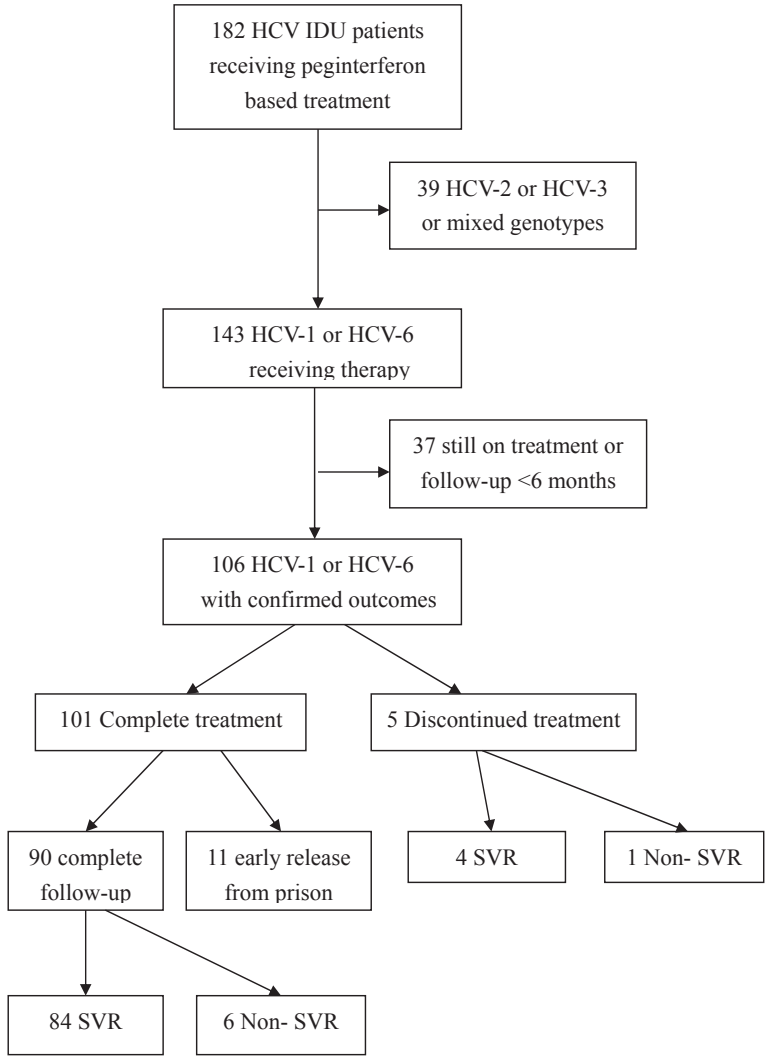

Figure 1. The flow chart and clinical outcome of the enrolled incarcerated HCV injection drug users.

flu-like symptoms). Eleven (10.4%) patients who complete treatment were lost to off-therapy follow–up due to early release or prison transfer (Figure 1). The baseline demographics, hemogram, serum creatinine level, and HCV viral load were comparable between patients with HCV-1 and HCV-6 infection. The meal alanine aminotransferase (ALT) level in HCV-6 patients were significantly higher than that in HCV-1 patients. Three HCV-1 and 2 HCV-6 patients prematurely discontinued treatment (p=0.97 and 7 HCV-1 and 4 HCV-6 (p=0.42) patients were lost to off-therapy follow–up due to early release from the prison.

The on-treatment RVR rate is higher in HCV-6 than HCV-1 patients who received at least one dose peginterferon/ribavirin (64% vs 41%, p=0.018), and who completed full course peginterferon/ribavirin therapy (64% vs 60%, p=0.023). The EVR and EOTVR were 100% in patients who received at one dose or completed full course therapy. The off-therapy SVR rate of HCV-6 is comparable with HCV-1 in patients receiving at least one dose regimen (100% vs 89%, p=0.16) and completing full course therapy (100% vs 91%, p=0.195) (Figure 2A and 2B).

Figure 3 showed the virologic responses in HCV-1 and HCV-6 patients who achieved and did not achieve RVR by response-guided peginterferon/ribavirin. In the RVR group receiving 24 weeks

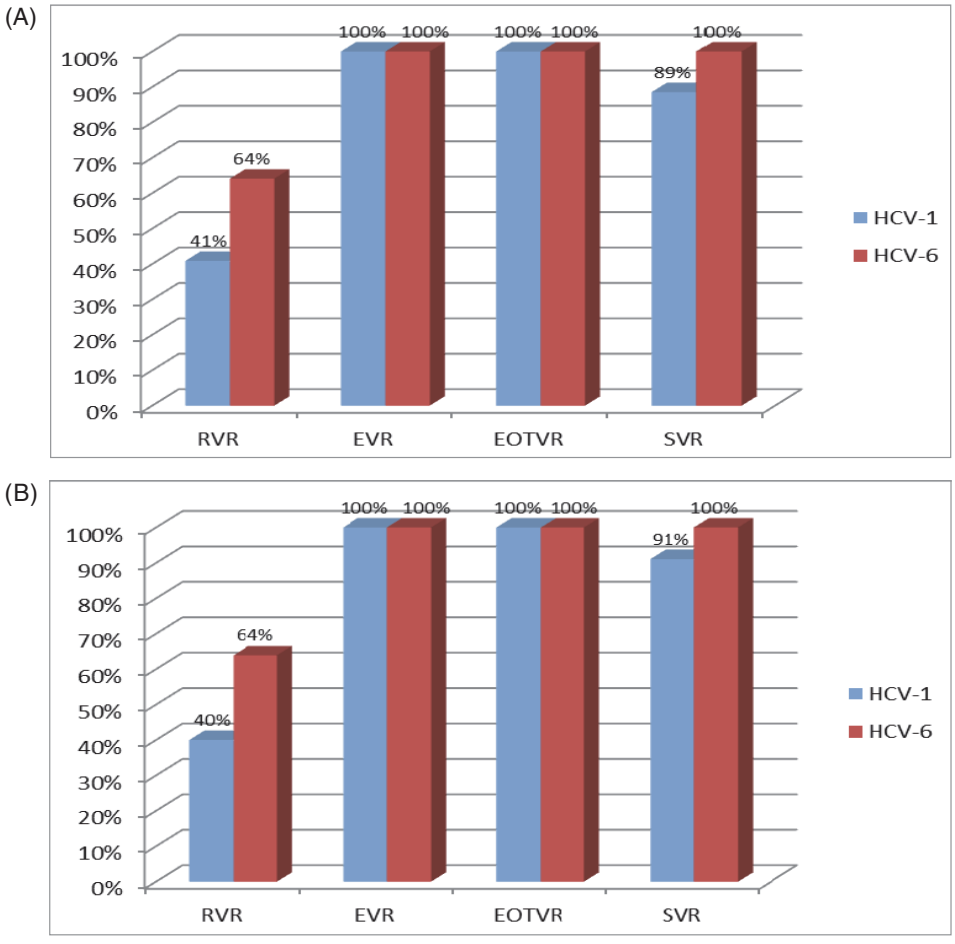

Figure 2. (A) The on-treatment and off-therapy virologic response in HCV-1 and HCV-6 patients receiving at least one dose of peginterferon/ribavirin treatment. (B) The on-treatment and off-therapy virologic response in HCV-1 and HCV-6 patients who completed full course of treatment by response-guided peginterferon/ribavirin therapy.

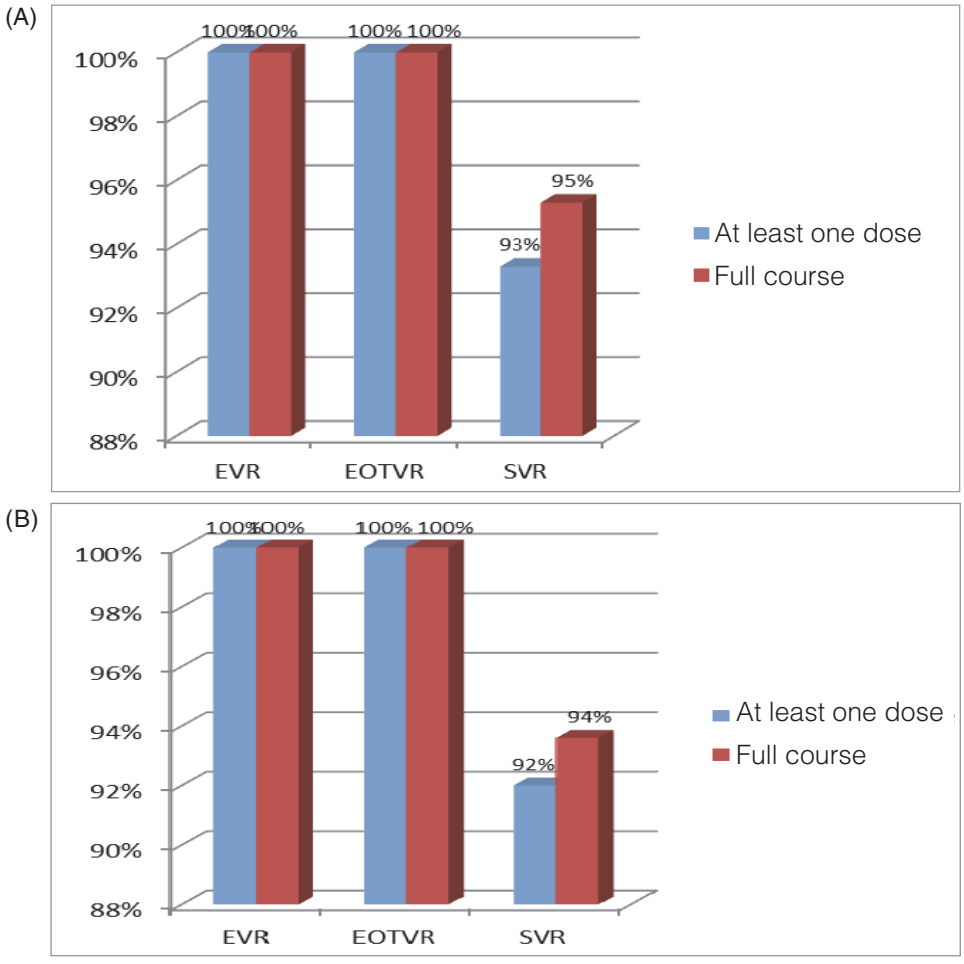

Figure 3. (A) The virologic responses in HCV-1 and HCV-6 patients who achieve RVR by response-guided peginterferon/ribavirin therapy. (B) The virologic responses in HCV-1 and HCV-6 patients who did not achieve RVR by response-guided peginterferon/ribavirin therapy.

Table 1. Characteristics of HCV-1 inmates and HCV-6 inmates

	Genotype 1(N=67)	Genotype 6(N=39)	P value
Male, n (%)	67 (100%)	39 (100%)	
Age (years)	39.6 (6.5)	39.2 (5.2)	0.08
Body weight (Kg)	70.0 (11.1)	72.4 (11.5)	0.91
ALT(IU/L)	89 (39)	101 (56)	0.02
Creatinine (mg/dL)	1.07 (0.12)	0.92 (0.14)	0.06
WBC (cells/uL)	6768 (1814)	7156 (1793)	0.71
Hb (g/dL)	15.4 (1.2)	15.5 (1.04)	0.68
Platelets (103cell/uL)	223 (59)	215 (46)	0.46
Log10 HCV IU/mL	5.81 (1.27)	5.99 (1.18)	0.38
RBV dose (mg/day)	1020 (160)	1020 (180)	0.68
Premature withdrawal of therapy, n (%)	3 (4.5)	2 (5.1)	0.97
Missing follow-up due to early release, n (%)	7 (10.4)	4 (10.3)	0.42

* RBV: ribavirin, ALT: alanine aminotransferase, WBC: white blood cell count, Hb: hemoglobin.
**Data was shown in mean (SD) unless otherwise indicated.

of peginterferon/ribavirin regimen, the EVR and EOTVR were 100%, and the SVR rate was comparable between patients receiving at least one dose therapy and completing full course therapy (95% vies 93%, p=0.21) (Figure 3A). Otherwise, in the Non-RVR patients receiving 48 weeks of therapy, the EVR and EOTVR were also 100%, and the SVR was also comparable in patients receiving at least one dose and completing full course treatment (94% vies 92%, p=0.20) (Figure 3B).

Discussion

Although HCV-1b is the predominant genotype infection in Taiwan, HCV-1a infection is the predominant one in our incarcerated patients with IDU, probably related to the different route of viral transmission. The genotype/subtype distribution in our patients was in line with a survey in Taiwan for HIV-infected IDU, showing high prevalence of HCV-1a and HCV-6 infection in these patients.[15] Although interferon-free direct acting antiviral agents (DAAs) are the mainstay of therapy for patients with HCV infection, the government in Taiwan only reimburses to patients with advanced hepatic fibrosis or cirrhosis, which is seldom found in young HCV inmates. Therefore, peginterferon/ribavirin may serve as an alternative option for these patients. albeit the anticipated treatment-emergent adverse as well as lengthy treatment duration. Recently, the use of generic pangenotypic agents for HCV, sofosbuvir/velpatasvir, has showed the excellent safety and efficacy, and this relative inexpensive treatment may also serve as another treatment option of inmates who are affordable to such treatment[25].

The viral response of HCV-6 to peginterferon/ribavirin therapy is rarely reported due to its lower prevalence around the world; these studies were of limited sample size and mostly reported from southeast Asia. In 2008, the first study of 48-weeks of peginterferon/ribavirin effect on HCV-6 in Hong Kong residents revealed better SVR than HCV-1[20]. Later, Tsang et al. also reported superior SVR in HCV-6 than HCV-1 and Tangkijvanich et al. reported good SVR in HCV-6 with 48-weeks of peginterferon/ribavirin regimen in Hong Kong and Thailand, respectively[26,27]. An American study of HCV-6 treatment over 48-weeks with peginterferon/ribavirin also favored better viral response in HCV-6 vs. HCV-1, which was compatible with HCV-2 or 3). Regarding the effect for shorter treatment duration of peginterferon/ribavirin, a multicentered randomized control study in the United States showed no difference between 24-weeks and 48-weeks[21].

By response guided peginterferon/ribavirin therapy, the SVR of 88% was achieved in HCV-6 patients in a Thailand study[27]. More recently, an excellent SVR of 90.3% was achieved for HCV-6 therapy, which was better than HCV-1 with 48-weeks of peginterferon/ribavirin therapy in Hong Kong; the impact of IL 28 on treatment outcome was not significant in HCV-6 due to its high SVR[28]. In our study the SVR is also excellent for HCV-1 and HCV-6 in patients who achieved RVR (91% vs 100%) and those who did not achieve RVR (89% vs 100%). The peginterferon/ribavirin should be safe to treat the non-cirrhotic incarcerated HCV-1 or HCV-6 patients with IDU for the low premature discontinuation rate 4.7% and the SVR is up to 80% even without full course therapy.

Although our study showed HCV-6 patients had comparably a high SVR rate to HCV-1 patients, several limitations existed. First, the numbers of enrolled patients were relatively small, and further studies are needed to validate our findings. Second, factors which potentially affected the treatment response, e.g. host interleukin-28 (IL28B) genotypes, stage of hepatic fibrosis, body's mass index, lipid profiles, were not available in this retrospectively study. Third, our study did not evaluate patients infected other than HCV-1 or 6 and patients with established cirrhosis. Based on the good safety

and efficacy profiles, treatment of peginterferon/ribavirin is feasible for non-cirrhotic incarcerated HCV- or HCV-6 patients with IDU, particularly for those who cannot meet the governmental reimbursement criteria for DAAs or be affordable to generic DAAs.

Conflict

No conflict of interests.

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靜脈注射藥癮受刑人C型肝炎第六型之治療效果，與第一型之比較

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摘 要

在台灣，第6型C型肝炎(HCV-6)少見於社區患者，然而 在靜脈注射藥癮受刑人C型肝炎中約有28%是第六型，因為矯正機關缺乏醫療照護，故國內第6型的治療經驗有限。自2013二代健保開始惠及受刑人之醫療照護，直到2017年底於高雄與屏東矯治機關，共有182位受刑人接受長效型干擾素併用雷巴威靈治療C型肝炎---HCV-1a, HCV-1b, HCV-6與其他型(2，3或mixed感染)之佔比分別29.6%, 24.1%, 24.7%, 與21.4%。扣除第2，3型或混和型，與仍在治療追蹤者，共有39位HCV-1與67位HCV-6共106位靜脈注射藥癮受刑人納入研究比較，本研究採回溯性分析HCV-1與HCV-6兩組人口學特徵，檢驗值，病毒量，治療後結果SVR；HCV-1與HCV-6皆為男性，皆靜脈注射藥癮者，年齡，體重，白血球數，血色素，血小板數，肌酐酸與病毒量，兩組無差異。雷巴威靈劑量，中斷率，兩組無差異，但HCV-6有較佳快速病毒反應RVR，與高病毒清除率。第6型C型肝炎受刑人干擾素治療之療效，如同文獻報告極優，不亞於第1型。觀之國內受刑人C型肝炎以第1，6型為主，加上兩型干擾素治療SVR相當高，以及醫療費用考量DDA無法應用，故在接受矯正服刑期間干擾素不失為治療C型肝炎的良方。