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Original Article

Relationship between application time and dosage of ribavirin and its antiviral efficacy on chronic hepatitis C

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Abstract: Object: To discuss the relationship between application time and dosage of ribavirin and its antiviral efficacy on chronic hepatitis C. Method: 69 patients with chronic hepatitis C were treated with pegylated interferons (Peg-IFN) α-2a combined with ribavirin, and their hemoglobin (HGB) reduced to 100 g/L after the treatment; they were divided into a group whose dosage was kept under strict regulation (hereinafter called the restricted group, n=35) and a group whose dosage was more relaxed (hereinafter called the relaxed group, n=34). Then, the virological response (SVR), recurrence rate, adverse drug reaction rate, etc. of the two groups were observed. Results: SVR in the relaxed group was significantly higher than that of the restricted group (P=0.048), and the difference in recurrence rates between the two groups had statistical significance (P=0.038). Compared to patients with HCV RNA>5 $\log_{10}$ copy/mL, the SVR of patients with HCV RNA<5 $\log_{10}$ copy/rnl significantly increased (P=0.021). The SVR of patients infected with non-genetic type-1 HCV receiving the full course of ribavirin was higher than those infected with genetic type-1 HCV (P=0.005). Conclusion: When anemic patients with chronic hepatitis C were treated with Peg-IFN α-2a combined with ribavirin, the sustained virological response could be improved and the recurrence of hepatitis C could be reduced by broadening the adjustment of the ribavirin dose. Moreover, patients infected with non-genetic type-1 HCV with low virus load were much more suitable for a relaxed adjustment of the ribavirin dose.

Keywords: Ribavirin, interferon, hepatitis

Introduction

At present, the standard therapeutic schedule of interferon (IFN) combined with ribavirin can cure 70%~90% patients with chronic hepatitis C (CHC) [1, 2]. If CHC does not receive standardized treatment, however, the chronic rate can be as high as about 85%. About 15%~20% patients infected with HCV will develop liver cirrhosis within 5 five years [3], and this ratio will increase to 25% in 10~20 years. Therefore, CHC severely threatens the survival rate of patients [4]. The major factors for patients who cannot have standardized treatment are adverse reactions to interferon and ribavirin. Treatment with either common IFN or pegylated interferons (Peg-IFN) combined with ribavirin can significantly improve the sustained virological response (SVR) and reduce the recurrence [5, 6]. Therefore, a sufficient dose and full course of ribavirin application in treatment are crucial [7, 8]. When antivirus treatment is combined with ribavirin, however, patients may have hemolytic anemia, fatigue, pruritus, rash, gout and other adverse reactions [9]. In particular, the ribavirin dose should be reduced when hemoglobin is significantly decreased; as a result, the curative effect of the antivirus treatment is affected [10]. When hemolytic anemia occurs, how much of the hemoglobin could be reduced without the reduction of the ribavirin dose, which could increase SVR without increasing patient risk? Exploratory clinical research on this topic will be conducted in this work and is reported as follows.

Data and methods

General data

326 patients with chronic hepatitis C treated by Peg-IFN combined with ribavirin from August 2009 to August 2012 were collected, including 115 patients having an interferon dose adjustment or withdrawal for adverse reactions (such as reduction of haem ameba and blood platelet counting) and 142 patients excluded from research for the hemoglobin reduction not

Table 1. Baseline characteristics of patients in two groups

Group	Sex (Man: Woman)	Age (years)	ALT (U/L)	HCV RNA (log_{10} copy/mL)	Virus genotyping (type-1 and non-type-1)	Baseline HGB (g/L)
Restricted group (n=35)	19:16	42.03±7.55	55.87±25.10	5.23±1.14	14:21	139.79±10.87
Relax group (n=34)	21:13	43.56±6.91	51.83±28.83	5.31±1.42	15:19	138.94±10.16
P	0.531	0.738	0.21	0.827	0.729	0.941

Table 2. Comparison of SVRs and recurrence between two groups (n, %)

Group	SVR (%)	Recurrence (%)
Restricted group (n=35)	26 (74.29)	6 (23.07)
Relax group (n=34)	31 (91.17)	2 (6.45)
χ^2	3.425	4.329
P	0.048	0.038

under 100 g/L in antivirus treatment. 69 patients with hemoglobin reduced to 100 g/L in treatment were divided into groups as observational populations in this research, including 35 patients in the group under strict adjustment of dosage (hereinafter called the restricted group) and 34 patients in the group of relaxed adjustment dosage (hereinafter called the relaxed group). For the restricted group, when hemoglobin decreased to ≤100 g/L, ribavirin was reduced (reduction refers to ribavirin reduced to 200 mg/d with every 10 g/L decrease of HGB); when HGB≤80 g/L, withdrew the drug. For the relaxed group, when HGB≤100 g/L, the ribavirin dose was not adjusted; when HGB≤80 g/L, reduced the dose; when HGB≤60 g/L, withdrew drug. After all the patients had ribavirin withdrawal, Peg-IFN mono-therapy was applied until the course ended.

Therapeutic methods

CHC patients were all subject to the diagnosis standard in the Expert Consensus of Chronic Hepatitis C Antivirus Treatment regulated in 2009 [11]. All the CHC patients were treated according to the following plan. Patients infected with non-genetic type-1 HCV were treated with ribavirin in doses of 800 mg/d combined with Peg-IFNα-2a 180 μg/week in a course lasting 24 weeks. Patients infected with genetic type-1 HCV were treated with ribavirin in doses of 1000 mg/d combined with Peg-IFN α-2a 180 μg/week for those with a body mass ≤75 kg and with ribavirin in a dose of 1200 mg/d for those with a body mass >75 kg in a course lasting 48 weeks.

Observational index

Liver and kidney function detection, routine blood examination, thyroid function, blood sugar, auto-antibody, routine urine test and viral genotyping were conducted before treatment. One month after treatment, routine blood examinations were conducted every week (including reticulocyte counting). Later, it was conducted every month until the treatment ended. HCV RNA was detected every three months before, during, and after the treatment; and was detected at the end of the treatment. Hepatic and renal functions were inspected every month, and thyroid function, blood sugar and auto-antibodies were detected every 3 months during treatment. Major observational indices included SVRs, recurrence rates and adverse reaction occurrence rates of both groups. SVR means that HCV RNA shows negative in retests 24 weeks after treatment. Recurrence means that although SVR is found, HCV RNA is still present after treatment. Major adverse reactions refer to heavy anemia that is, HGB<60 g/L, and the occurrence of cardiovascular events (including stenocardia, myocardial infarction and arrhythmia), as well as fatigue, dizziness, palpitations, etc. are also included.

Statistical methods

SPSS19.0 software was used in statistical analysis. Enumeration data were described with case number or percentage, measurement data were expressed with mean ± standard deviation ($\overline{x}\pm s$) or mean value (range). Moreover, an f test should be conducted for independent samples and χ^2 test for matching enumeration data. P<0.05 means that the difference has statistical significance.

Results

Baseline characteristics of the two groups

The difference between the two groups had no statistical significance in respects of sex ratio,

Table 3. Comparison of Occurrence of Adverse Reaction between Two Groups (n, %)

Group	Moderate anemia (%)	Cardiovascular event (%)	Weak	Dizziness	Palpitation	Amaurosis
Restricted group (n=35)	1 (2.86)	2 (5.71)	25 (71.43)	20 (57.14)	15 (42.86)	3 (8.57)
Relax group (n=34)	3 (8.82)	4 (11.76)	19 (55.88)	16 (47.06)	11 (32.35)	1 (2.94)
χ^2	1.124	1.766	1.329	1.574	2.988	2.543
P	0.296	0.183	0.267	0.482	0.074	0.156

Table 4. The subgroup analysis on the characteristics of the population of the restriction group and the number of the virus were divided

Observation index	Patients (n)	SVR	χ^2	*P*
HGB (g/L)				
120~140	16	87.5	0.508	0.476
>140	18	94.44		
HCV RNA (log_{10} copy/mL)				
>5	13	76.92	5.315	0.021
≤5	12	100		
Sex				
Male	21	90.48	0.033	0.855
Female	13	92.31		
Genetic typing				
Type-1	15	86.67	0.679	0.41
Non-type-1	19	94.74		
Proportion of patients receiving full-course ribavirin treatment				
Type-1	10/15	70	7.897	0.005
Non-type-1	15/19	100		

age, ALT, virus load, virus genotyping and baseline HGB level. **Table 1** showed the baseline characteristics of the two groups. During antiviral treatment, however, the lowest levels of HGB in both groups showed a difference. The medium HGB level in the restricted group was significantly higher than that in the relaxed group (85.36±9.24 vs. 77.87±15.85, $P<0.05$). Among non-genetic type-1 patients, the medium time of ribavirin application in the relaxed group was up to 23.05 weeks, while in contrast it was only 21.67 weeks in the restricted group with a difference of statistical significance. On the contrary, the time of ribavirin application for genetic type-1 patients showed no significant difference. In the relaxed group, there were 66.67% genetic type-1 patients and 78.95% non-genetic type-1 patients who completed the full course of ribavirin application, while the ratios in the restricted group were only 42.86% and 61.90% with a difference of statistical significance.

Comparison of SVRs, recurrence rates and occurrence rates of adverse reaction between the two groups

Patients in the two groups had medicine withdrawn and were followed-up for 6 months after treatment. The results showed that SVR in the relaxed group was significantly higher than that of the restricted group (91.17% vs. 74.29, $\chi^2=3.425$, $P=0.048$). In the continuing follow-up after receiving SVR, 2 patients having a recurrence were found in the relaxed group and 6 in the restricted group. It showed that the recurrence rate in the restricted group was also significantly higher than that of the relaxed group with a difference of statistical significance (23.07% vs. 6.45, $\chi^2=4.239$, $P=0.038$) as shown in **Table 2**. For patients in both groups, the proportion of patients having heavy anemia in the relaxed group was higher than that in the restricted group without any difference of statistical significance (8.82% vs. 2.86%, $P=0.296$). During the treatment, there

was one patient who had angina during treatment and one who had arrhythmia in the restricted group; there was one patient who had angina and three who had arrhythmia in the relaxed group. The occurrence of weakness, dizziness and palpitations in the relaxed group were slightly higher than that of the restricted group without any difference of statistical significance as shown in **Table 3**.

Subgroup analysis on SVR and baseline characteristics of the relaxed group

The SVR of the relaxed group was relatively high, up to 91.17%, so subgroup analysis was conducted for the relationship between SVR and baseline characteristics. In this analysis, the difference of baseline HGB level, sexual condition and genetic typing had no relationship to SVR. However, when baseline HCV RNA<5 $\log_{10}$ copy/mL, SVR rate could be up to 100%, and when baseline HCV RNA>5 $\log_{10}$ copy/Ml, SVR was 76.92% with statistically significant difference (χ^2=5.315, *P*=0.021). It indicated that the curative effect on patients with a low baseline viral load was much better after relaxing the restriction of ribavirin. Among 15 genetic type-1 patients, there were 10 patients who received the full-course of treatment for 48 weeks, and the SVR for these patients was 70%. Among the 19 non-genetic type-1 patients, there were 15 patients who received the full-course of treatment after appropriately relaxing the restriction of the ribavirin dose, and the SVR for these patients was 100%. Therefore, SVR for non-genetic type-1 patients who received a full-course of treatment with ribavirin was higher than that of genetic type-1 patients (χ^2=7.897, *P*=0.005). It indicated that appropriate relaxation of restriction can realize better curative effect for non-genetic type-1 patients as shown in **Table 4**.

Discussion

Medical science-backed evidence shows that HCV can be effectively eliminated by combining interferon with ribavirin to improve the quality of life and long-term survival rate of patients and reduce the occurrence of HCV-related liver cirrhosis, hepatic failure and liver cancer [12]. The 24th week after drug withdrawal is the key node to determine the antivirus effect on chronic hepatitis C, and more than 90% of occurrences manifest within the first 12 weeks after drug withdrawal. If patients are followed up for 5 years for those who got SVR 24 weeks after drug withdrawal, more than 90% of patients can keep disease stable [13]. Therefore, the key point in reducing the recurrence of hepatitis C is to improve the SVR rate. As an important drug in a combined therapeutic schedule, ribavirin can effectively prevent the breakthrough and recurrence of the disease, so it is crucial in improving SVR [14]. Reference reported that SVR is brought about in 59% of cases by treating HCV with simple pegylated interferons for 12 months, while SVR can increase to 64%~76% by combining treatment with ribavirin for 12 months [15, 16]. Among patients having recurrence of HCV infection who were treated with simple interferon, almost half of them can obtain SVR after being treated with additional ribavirin for 24 weeks in the second round of treatment [17]. All the evidence listed above proves the importance of ribavirin in the treatment of chronic hepatitis C. However, ribavirin has adverse effects in the antivirus treatment and hemolytic anemia is its most common form. The reference had reported that when the ribavirin dose >15 $mg \cdot kg^{-1} \cdot d^{-1}$, the occurrence rate of hemolytic anemia is dose dependent [18], so, the occurrence has become an important factor which will affect full-course treatment with ribavirin for hepatitis C, and physicians should reduce or withdraw ribavirin according to the progress of the disease. Some researchers have shown that there are relationships between an accumulative dose of ribavirin and SVR. When accumulative dose ≥80%, SVR significantly increased [19]. Thus, it is the emphasis of clinical researches to prolong the time of combining treatment as long as possible to obtain a high SVR and low occurrence rate of adverse reaction.

At present, it is recommended by domestic and overseas guidelines [20] that when anemia occurred in ribavirin application, ribavirin should be reduced when HGB decreased to ≤100 g/L and withdraw when HGB≤80 g/L. In early clinical observations, however, better curative effects can be achieved without reducing the ribavirin dose under close monitoring of routine blood when patients have slight anemia. We will not reduce the dose when HGB≤100 g/L, reduce the dose when HGB≤80 g/L, and withdraw the drug when HGB≤60 g/L in combining treatment with ribavirin, and the

difference will be compared with the above standards in viral response. In this work, there were 66.67% (genetic type-1) and 78.95% (non-genetic type-1) patients having a full-course of ribavirin treatment in the relaxed group, respectively. However, there were only 42.86% (genetic type-1) and 61.9% (non-genetic type-1) patients having the full-course of ribavirin treatment in the restricted group, respectively. We also found that after relaxing the adjustment of the ribavirin dose for anemia, SVR is significantly higher than that of the restricted group. In the continuing follow-up after achieving SVR, the recurrence rate of the relaxed group is also significantly lower than that of the restricted group. For patients in both groups, though the ratio of heavy anemia and the occurrence rate of cardiovascular events, as well as weakness, dizziness and other symptoms in the relaxed group are higher, the difference is not of statistical significance.

In addition, we also analyzed the correlation between partial baseline characteristics and SVR in the relaxed group. We found that the difference of baseline HGB level, sex and genetic typing had no relationship to SVR in this group. However, when the baseline HCV RNA<5 $\log_{10}$ copy/mL, the SVR of patients significantly increased compared with that when baseline HCV RNA>5 $\log_{10}$ copy/mL. Moreover, compared with the SVR of genetic type-1 patients, the SVR of non-genetic type-1 patients were higher after receiving a full-course of treatment with ribavirin. It indicated that relaxing restriction of the ribavirin dose adjustment is suitable for non--genetic type-1 patients with a low viral load to effectively improve the curative rate of hepatitis C. However, this work is limited to just a few research cases, when conducting statistical analysis, the increase of any event may lead to a different statistical result, so the result may be incorrect. Even so, our preliminary research still provides thoughts and evidence to assist in large-scale in-depth research in the future.

Disclosure of conflict of interest

None.

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References

[1] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus fibavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet 2001; 358: 958-965.

[2] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982.

[3] Lau G, Zhuang H. Top hepatology issue in China. J Gastroent Hepatol 2013; 17: 9-10.

[4] Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002; 36: 35-46.

[5] McHutchison JG, Poynard T. Combination therapy with interferon plus fibavifin for the initial treatment of chronic hepatitis C. Semin Liver Dis 1999; 19: 57-65.

[6] Krawitt EL, Ashikaga T, Gordon SR, Ferrentino N, Ray MA, Lidofsky SD; New York New England Study Team. Peginterferon alfa-2b and ribavirin for treatment-refractory chronic hepatitis C. J Hepatol 2005; 43: 243-9.

[7] Reddy KR, Shiffman ML, Morgan TR, Zeuzem S, Hadziyannis S, Hamzeh FM, Wright TL, Fried M. Impact of ribavirin dose reductions in hepatitis C virus genotype I patients completing peginterfemn alfa -2a/ribavirin treatment. Clin Gastroenterol Hepatol 2013; 5: 124-129.

[8] Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM; PEGASYS International Study Group. Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2014; 140: 346-355.

[9] Fried MW. Side effects of therapy of hepatitis C and their Management. Hepatology 2002; 36: 237-244.

[10] Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, Wright T, Younossi Z, Goon BL, Tang KL, Bowers PJ; Proactive Study Group. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. Gastroenterology 2004; 126: 1302-1311.

[11] Committee of Experts on Antiviral Therapy of Chronic Hepatitis C. Experts consensus on an-

tiviral therapy of chronic hepatitis C. Chin J Exp Clin Infect Dis (Electronic Edition) 2009; 3: 343-352.

[12] Oze T, Hiramatsu N, Yakushijin T, Kurokawa M, Igura T, Mochizuki K, Imanaka K, Yamada A, Oshita M, Hagiwara H, Mita E, Ito T, Inui Y, Hijioka T, Tamura S, Yoshihara H, Hayashi E, Inoue A, Imai Y, Kato M, Yoshida Y, Tatsumi T, Ohkawa K, Kiso S, Kanto T, Kasahara A, Takehara T, Hayashi N. Pegylated interferon alpha-2b (PegIFNa-2 b) affects early virologic response dose-dependently in patients with chronic hepatitis C genotype 1 during treatment with Peg-IFN a-2b plus ribavirin. J Viral Hepat 2019; 16: 578-585.

[13] Oze T, Hiramatsu N, Yakushijin T, Kurokawa M, Igura T, Mochizuki K, Imanaka K, Yamada A, Oshita M, Hagiwara H, Mita E, Ito T, Inui Y, Hijioka T, Tamura S, Yoshihara H, Hayashi E, Inoue A, Imai Y, Kato M, Yoshida Y, Tatsumi T, Ohkawa K, Kiso S, Kanto T, Kasahara A, Takehara T, Hayashi N. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology 2010; 139: 1593-1601.

[14] Mutimer D. Ribavirin with interferon for hepatitis C in dialysis patients: efficacious and safe in the right patients in good hands. Gut 2015; 64: 190-191.

[15] Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, Heathcote J, Zeuzem S, Trepo C, Albrecht J. Randomised trial of interferon alpha2b plus fibavirin for 48 weeks or for 24 weeks verses interferon alpha2b pins placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group 0rnT. Lancet 1998; 352: 1426-1432.

[16] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: arandomised trial. Lancet 2013; 35: 958-967.

[17] Heathcote EJ, James S, Mullen KD, Hauser SC, Rosenblate H, Albert DG Jr. Chronic hepatitis C virus patients with breakthroughs during interferon treatment can successfully be retreated with consensus interferon. The Consensus Interferon Study Group. Hepatology 1999; 30: 562-566.

[18] Maddrey WC. Safety of combination interferon alfa-2b/ribavirin therapy in chronic hepatitis C-relapsed and treatment-naïve patients. Semin Liver Dis 1999; 19: 67-75.

[19] Sun LJ, Yu JW, Kang P, et al. Impact of fibavirin cumulative dose on virological response rates in genotype 1 hepatitis C virus infected patients. Chin J Infect Dis 2011; 29: 413-417.

[20] European Association for Study of Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol 2014; 60: 392-420.