Antiviral Efficacy and Influencing Factors of Hcv Recurrence after Liver Transplantation

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Abstract: Objective: To analyze the antiviral efficacy and influencing factors of HCV recurrence after liver transplantation. Methods: 42 patients with HCV recurrence after liver transplantation in our hospital from February 2020 to February 2021 were retrospectively selected, and the clinical efficacy of different treatment methods was statistically analyzed. Results: Among the 21 patients, 16 (76.2%) got etvr, and the other 5 patients who didn't get etvr were treated for less than 3 months. Among the 16 patients with etvr, 11 patients had virus rebound after drug withdrawal, and 5 patients (23.8%) had SVR. Etvr was obtained in both standard treatment and foot course treatment, and in incomplete treatment, etvr was obtained in 7 cases, but there was no significant difference among the 3 groups ($P > 0.05$). SVR was obtained in 4 cases of standard treatment, 1 case of foot treatment, and no case of incomplete treatment. The difference was statistically significant ($P < 0.05$). There were significant differences in viral load and treatment plan between the two groups, indicating that viral load before treatment and the dose and course of antiviral drugs were important factors affecting the SVR ($P < 0.05$). In the course of antiviral treatment, the patients had fever and influenza like symptoms, joint discomfort and loss of appetite, but they were tolerable and did not affect the treatment. Twenty patients had to use G-CSF to maintain antiviral therapy due to neutropenia, and two patients developed autoimmune hepatitis at the end of treatment. The reasons for discontinuation were rejection (4 cases), severe neutropenia (4 cases), biliary complications (4 cases), decreased hemoglobin (2 cases), extreme fatigue (2 cases), skin healing (2 cases), skin pain and itching (2 cases), infection (2 cases) and self discontinuation (2 cases). After stopping antiviral treatment and giving corresponding symptomatic treatment, the symptoms of all patients were eliminated and the biochemical indexes were improved. Conclusion: The antiviral effect of HCV recurrence after liver transplantation is significant. The influencing factors are the viral load before treatment, the dose and course of antiviral drugs.

1. Introduction

At present, the end-stage liver disease caused by HCV infection is one of the main reasons for liver transplantation, but the recurrence of hepatitis C is an important reason for the decline of liver function or affecting the quality of life of patients after liver transplantation[1]. If hepatitis C relapses after transplantation, the progression of liver injury is significantly faster than that of non transplant patients, and the incidence of liver cirrhosis within 5 years is 30%[2]. Effective antiviral therapy can prevent or delay the progression of the disease. Therefore, it is very important to study the antiviral treatment of hepatitis C recurrence after liver transplantation[3]. This study analyzed the antiviral efficacy and influencing factors of HCV recurrence after liver transplantation.

2. Materials and Methods

2.1 General Information

42 patients with HCV recurrence after liver transplantation in our hospital from February 2020 to

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February 2021 were retrospectively selected, aged from 31 to 71 years old, with an average of (51.3 1 ± There were 12 females (28.6%) and 30 males (71.4%). In terms of HCV RNA gene, 38 cases (90.5%) were type 1b and 4 cases (9.5%) were type 2A; In terms of treatment methods, 10 cases (23.8%) received standard treatment, 8 cases (19.1%) received foot treatment, and 24 cases (57.1%) received incomplete treatment.

2.2 Inclusion and Exclusion Criteria

Inclusive criteria: 1) all patients were HCV related end-stage liver disease; 2) All patients received orthotopic liver transplantation; 3) HCV RNA was positive after operation; 4) Liver biopsy confirmed the recurrence of hepatitis C. Exclusion criteria: 1) biliary complications, rejection and other common postoperative complications; 2) HBC and EBC infection; 3) There are contraindications to interferon treatment[4].

2.3 Methods

2.3.1 Antiviral Therapy

Interferon combined with ribavirin small dose incremental regimen for antiviral treatment. The initial dosage of interferon (ganleneng, xianlingzaoya, batch No. 010l30201) was 900000 units / time, once / 2D, and the initial dosage of ribavirin was 600 mg / d. If the patient can tolerate the treatment, increase the drug dose once every 2 weeks, and gradually transition to the standard long-acting interferon (pegasyn, Roche, batch number 81182) combined with ribavirin treatment, so as to achieve the maximum tolerated dose or standard treatment dose of the patient. In the course of treatment, such as granulocyte < 1.0 × 109 / L, then given granulocyte colony stimulating factor (G-CSF) symptomatic treatment. If the patient has serious adverse reactions (such as rejection, severe infection, mental disorders and uncontrollable complications), the antiviral treatment should be stopped. The standard course of treatment was 48 weeks for genotype 1 and 24 weeks for genotype 2.

2.3.2 Immunosuppressive Program

Some patients were given methylprednisolone + tacrolimus + mycophenolate acetate triple immunosuppressive regimen in the early stage of transplantation, and methylprednisolone was stopped within 3 months after transplantation. After 3 months, tacrolimus alone or combined with mycophenolate was used according to the patient's condition.

2.3.3 Therapeutic Method

Standard treatment: PEG IFN α- The treatment time was 48 weeks for genotype 1 and 24 weeks for genotype 2. Foot treatment: interferon and ribavirin dose did not meet the standard treatment dose, but completed 24 or 48 weeks of treatment. Incomplete treatment: the dose of interferon and ribavirin failed to reach the standard treatment dose, and failed to complete 24 or 48 weeks of treatment.

2.4 Evaluation Criteria of Curative Effect

Rapid virological response (RVR): serum HCV RNA was lower than detectable level at 4 weeks after antiviral treatment; Complete early virological response (cevr): after 12 weeks of antiviral treatment, serum HCV RNA was lower than detectable level; End of treatment virological response (etvr): HCV RNA was lower than detectable level at the end of antiviral treatment; Sustained virological response (SVR): after 24 weeks of antiviral treatment, serum HCV RNA was lower than detectable level. RT-PCR was used to detect the serum HCV RNA load before and after treatment. The lowest detection value of HCV RNA was 100 IU / ml[5].

2.5 Observation Index

1) The influencing factors of SVR; 2) Adverse reactions in antiviral therapy.

2.6 Statistical Analysis

Spss20.0 statistical software was used for analysis, the measurement data was expressed with ($\bar{x} \pm s$), the comparison was performed with *t* test, the repeated measurement data was analyzed with ANOVA, the count data was expressed with rate (%), the comparison was performed with chi square test, $P < 0.05$ was considered as statistically significant.

3. Results

3.1 Comparison of Clinical Efficacy of Different Treatment Methods

Among the 21 patients, 16 (76.2%) got etvr, and the other 5 patients who didn't get etvr received antiviral therapy for less than 3 months. Among the 16 patients with etvr, 11 patients had virus rebound after drug withdrawal, and 5 patients (23.8%) had SVR. Etvr was obtained in both standard treatment and foot course treatment, and in incomplete treatment, etvr was obtained in 7 cases, but there was no significant difference among the 3 groups ($P > 0.05$). SVR was obtained in 4 cases of standard treatment, 1 case of foot treatment, and no case of incomplete treatment. The difference was statistically significant ($P < 0.05$). See Table 1.

Table 1 Comparison of Clinical Efficacy of Different Treatment Methods[n(%)]

Therapeutic methods	n	RVR	cEVR	ETVR	SVR
Standard treatment	10	6(60.0)	8(80.0)	10(100.0)	8(80.0)
Adequate treatment	8	4(50.0)	8(100.0)	8(100.0)	2(25.0)
Incomplete treatment	24	8(33.3)	8(33.3)	14(58.3)	0(0)
χ^2		0.760	18.550	0.860	16.010
P		>0.05	<0.05	>0.05	<0.05

3.2 Single Factor Analysis of Influencing Factors of Svr

There were significant differences in viral load and treatment plan between the two groups, indicating that viral load before treatment and the dose and course of antiviral drugs were important factors affecting the SVR ($P < 0.05$). See Table 2.

Table 2 Single Factor Analysis of Influencing Factors of Svr

Projects	Classification	n	Get SVR(n=10)	Not get SVR(n=32)	t/χ^2	*P*
Age (years)			51.4±6.7	51.2±9.6	1.638	>0.05
ALT(U/L)			74.5±10.1	65.7±10.4	1.886	>0.05
HCV RNA Gene	Type 1b	38	8(21.1)	30(79.0)	0.860	>0.05
	Type 2a	4	2(50.0)	2(50.0)		
Viral load	High	6	6(100.0)	0(0)	16.750	<0.05
	Low	36	4(11.1)	32(88.9)		
Therapeutic method	Standard treatment	10	8(80.0)	2(20.0)	14.450	<0.05
	Adequate treatment	8	2(25.0)	6(75.0)		
	Incomplete treatment	24	0(0)	24(100.0)		
Clinical effect	RVR	18	6(33.3)	12(66.7)	10.760	<0.05
	cEVR	24	4(16.7)	20(83.3)		

3.3 Adverse Reactions and Reasons for Termination of Treatment

In the course of antiviral treatment, the patients had fever and influenza like symptoms, joint discomfort and loss of appetite, but they were tolerable and did not affect the treatment. Twenty patients had to use G-CSF to maintain antiviral therapy due to neutropenia, and two patients developed autoimmune hepatitis at the end of treatment. The reasons for discontinuation were rejection (4 cases), severe neutropenia (4 cases), biliary complications (4 cases), decreased hemoglobin (2 cases), extreme fatigue (2 cases), skin healing (2 cases), skin pain and itching (2 cases), infection (2 cases) and self discontinuation (2 cases). After stopping antiviral treatment and giving corresponding symptomatic treatment, the symptoms of all patients were eliminated and the biochemical indexes were improved.

4. Discussion

Due to the particularity of liver transplantation, there is no standard antiviral therapy for hepatitis C recurrence after liver transplantation for HCV related end-stage liver disease. At present, interferon combined with ribavirin is still used for reference. A comprehensive study of 38 anti HCV treatments after liver transplantation showed that the etvr of IFN or PEG IFN combined with ribavirin was 34%, the SVR of PEG IFN combined with ribavirin was 42%, and the SVR was 20% and 24%, respectively. Another study, which combined 19 studies on PEG LFN combined with ribavirin, showed that etvr and SVR were 42% and 30% respectively[6]. Small dose incremental scheme is a treatment scheme that early gives small dose of interferon combined with ribavirin, gradually increases the dose of antiviral drugs according to the tolerance of patients, in order to enhance the tolerance of patients to drugs, and can closely monitor the adverse reactions of drugs. In this study, 76.2% (32 / 42) patients received etvr and 23.8% (10 / 42) patients received SVR.

Previous studies have found that patients with early virological response, low HCV RNA load before treatment, no previous antiviral therapy and non genotype 1 can obtain higher SVR. In addition, the dose and course of treatment of antiviral drugs are also important factors affecting the curative effect. In our study, 23.8% patients completed the standard antiviral protocol; 19.1% of the patients completed the antiviral treatment, but failed to reach the standard dose of antiviral drugs; Most patients (57.1%) were treated incompletely[7]. There was no significant difference in etvr acquisition rate among the three groups, but there was significant difference in SVR acquisition rate. Univariate analysis showed that the viral load before treatment and the dose and course of antiviral treatment were important factors affecting SVR acquisition. It is suggested that the dose and course of treatment of antiviral drugs are very important to the curative effect. There were 7 cases in the incomplete treatment group and 4 cases in the foot course treatment group respectively, but rebound occurred in the incomplete treatment group after drug withdrawal, and 3 cases (3 / 4) in the foot course treatment group, suggesting that even if etvr was obtained during treatment, if the standard dose and course of antiviral treatment could not be reached, rebound would easily occur after drug withdrawal[8]. Therefore, for patients with non-standard dose of antiviral therapy, whether the course of treatment can be extended to reduce rebound after drug withdrawal needs further study.

In 2011, the American Society for liver diseases has used protease inhibitors for the treatment of HCV genotype lb in non transplant population, but whether it can be used in post transplant population is still worth studying[9]. The meta statistical differences of RVR acquisition rate among the six groups may be due to the small number of cases and the differences of HCV load and genotyping meta before treatment. Due to the small number of cases in this group, we will continue to increase the sample size in the follow-up study in order to obtain more reliable conclusions. The main adverse reaction of interferon anti HCV therapy was neutropenia. In this study, 20 cases (47.6%) needed G-CSF to maintain antiviral therapy. G-CSF itself has no obvious effect on the antiviral efficacy, but it can increase the dosage of antiviral drugs and complete the course of treatment, so it can indirectly improve the antiviral efficacy. At present, there are different reports (0% - 25%) about the rejection induced by interferon combined with ribavirin after transplantation[10]. We found that the incidence of rejection was 9.5%. Because it can lead to serious adverse consequences, the occurrence of adverse reactions should be closely monitored in the process of antiviral treatment. Once it occurs, the course of treatment should be terminated, and the corresponding anti rejection treatment should be given. In this study, 4 cases of rejection were mild. After stopping antiviral therapy and adjusting anti rejection drugs in time, the rejection was controlled and the biochemical indexes returned to normal. It is suggested that the small dose incremental scheme is helpful to closely observe the adverse reactions of drugs and reduce the risk.

In conclusion, The antiviral effect of HCV recurrence after liver transplantation is significant. The influencing factors are the viral load before treatment, the dose and course of antiviral drugs.

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