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Role Of Interferon-Alpha 2b In Combination Therapy Of Chronic Hepatitis C Virus Infection

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Background &Aims

Hepatitis C contagion(HCV) reinfection after liver transplantation is frequent and leads to habitual hepatitis and cirrhosis. The use of antiviral remedy in this situation remains controversial. This study aimed to assess the safety and efficacity of interferon alfa- 2b plus ribavirin for intermittent hepatitis C following liver transplantation.

Methods: styles Transplant donors with intermittent habitual hepatitis C were randomized to admit either no treatment or remedy with interferon alfa- 2b(3 MU 3 times a week) plus 1000 – 1200 mg/ day ribavirin for 1 time. Cases were followed up for 6 months after the end of treatment. The primary end point was loss of HCV RNA 6 months after the end of treatment.

Results: Fifty- two cases were randomized(treatment, 28; placebo, 24). Sixteen cases were with-drawn from the study; 12(43) were from the treated group(substantially for anemia(7 cases)) and 4(17) from the control group. In the treated group, serum HCV RNA was undetectable in 9 cases(32) at the end of treatment and 6(21.4) at the end of the follow-up period, whereas no case in the control group lost HCV RNA at any point(P = 0.036 at the end of follow- up). still, there was no significant histologic enhancement.

Conclusions: The combination of interferon alfa- 2b plus ribavirin convinced a sustained virologic response in 21 of transplant donors with intermittent hepatitisC. still, 43 discontinued remedy due to adverse events(primarily severe anemia). Strategies to enable treatment with lower boluses of ribavirin need to be explored.

Nearly 300 million people worldwide are chronically infected with hepatitis C contagion(HCV). Between 20 and 30 of these cases will develop cirrhosis within 20 – 30 times. HCV- related end- stage cirrhosis is presently the leading suggestion for liver transplantation in Europe. Rush of HCV after transplantation is nearly universal, and 60 – 80 of cases will develop lesions of habitual hepatitis C on the graft. Recent data confirm that HCV infection impairs case and allograft survival The course of HCV graft complaint is

accelerated in transplant donors compared with immunocomplex roof cases, with reported 5- time rates of cirrhosis around 10 – 20and up to 28. This yields an redundant threat of death or transplantation for liver failure 10 – 15 times after transplantation. Given this threat, it seems reasonable to offer antiviral remedy to liver trans- factory donors who develop a rush of habitual hepatitis C. At the time this trial was designed, the optimal treatment for regular habitual hepatitis C was combination remedy with interferon alfa- 2b plus ribavirin, and this combination had promising results in 21 liver transplant donors with habitual hepatitis C on the graft. Cases with HCV reinfection of the graft after liver transplantation differ from immunocompetent cases in several ways. Their viral cargo is veritably high, and utmost transplant donors in Europe are infected with genotype 1; both factors are prophetic of a lower virologic response rate. Also, interferon alfa mono- remedy has been associated with a poor virologic response rate(< 10), and interferon remedy has been sometimes associated with severe acute or habitual rejection of the graft. The end of this phase 3, randomized, resemblant- group, multicenter, open-marker study was to estimate the efficacity and tolerability of combination remedy with interferon alfa-2b plus ribavirin for 12 months compared with standard care(experimental undressed control group) in liver transplant donors with habitual hepatitisC.

Accoutrements and styles

Selection of Cases

Adult first- time liver transplant donors from 2 French centers(Centre Hepatobiliary, Hospital Paul Brousseau, Villejuif, and Service hepatology, hostel- Dieu, Lyon, France) with rush of habitual hepatitis C on the graft were included from November 1997 to October 1998 in this phase 3, randomized, open- marker study if they fulfilled the following criteria. Eligible cases were progressed 18 to 70 times and passed transplantation for end- stage HCV-positive, hepatitis B sur-face antigen – negative liver complaint further than 6 months before study entry. All cases had histopathologic supporter proven habitual hepatitis defined by a METAVIR score18 exertion score ≥ 1 and fibrosis score ≥ F0 on a liver vivisection performed within 3 months before study entry, with serum HCV RNA descry- suitable by polymerase chain response(PCR), irrespective of liver enzyme situations(cases with normal liver enzyme situations were included). Cases had to be taking cyclosporine or tacrolimus with a stable immunosuppressive authority. Cases were barred if they met any of the following criteria former treatment with interferon after transplanta tion, transplantation for rejection or habitual hepatitis C on the graft, presence of an associated hepatocellular melanoma. ≥ 3 cm at histologic evaluation after transplantation, serum hepatitis B face antigen positivity, serum mortal immuno- insufficiency contagion positivity, an acute rejection occasion within the once 6 months or histologic features of rejection on screening vivisection(i.e., acute rejection, loss of further than 25 of interlobular corrosiveness tubes, centrilobular ischemia), undetermined biliary complications, serum creatinine position> 200 µmol/ L, γ- glutamyl transferase position> 20 × N(upper limit of normal), bilirubin position> 100 µmol/ L, neutrophil count< 1500/ mm3, platelet count.

Study Design

Eligible cases were aimlessly assigned to 1 of 2 groups in a 11 rate. One group entered interferon alfa – 2b 3 MU administered subcutaneously 3 times a week plus ribavirin administered orally doubly daily at a lozenge of 800, 1000, or 1200 mg/ day. The planned duration treatment was 48 weeks. The alternate group entered standard care with no antiviral treatment(experimental control group). In the treatment group, the lozenge of ribavirin was grounded on the subject's birth hemoglobin value. A lozenge of 800 mg/ day ribavirin was initiated if the hemoglobin value was ≥ 10 to< 12 g/ dL for women and ≥ 11 to< 13 g/ dL formen.However, ribavirin was initiated at a lozenge of 1000 mg/ day at body weight< 75 kg or 1200 mg

at body weight> 75 kg, If the hemoglobin value was ≥ 12 g/ dL in women & ≥ 13 g/ dL in men. The lozenge of ribavirin was increased from 800 mg/ day to the full lozenge of 1000 or 1200 mg/ day if the case' s hemoglobin value latterly met the protocol criteria. Use of an undressed experimental control group was supposed justified, because use of antiviral remedy for rush of habitual hepatitis C after transplan tation wasn't routine and there was no evidence that similar treatment could be salutary. All cases were followed up for 48 weeks during the treatment period plus 24 weeks after the end of remedy. A liver vivisection was performed in all cases during the webbing period within 3 months before study entry, at 24 weeks, at the end of treatment, and at the end of the follow-up period. Evaluation of the vivisection samples was performed by 2 elderly original pathologists(M.R. andM.C.). Results on the presence or absence of liver rejection were incontinently handed to the investigators to allow prompt operation of liver rejection. For the efficacity analysis, both pathologists were dazed with respect to patient identification, treatment group allocation, and time of the vivisection rela tive to treatment. METAVIR and Knodell scores were estimated by both pathologists, who reached a agreement each time their reading of the histology score differed.

Safety Monitoring

Adverse events and attendant specifics were re- corded at each visit. Cases randomized to the treatment group were assessed at weeks 1, 2, 4, 6, 8, 12, 16, 20, 24,,32, 40, 44, and 48 during treatment and at follow-up weeks 4, 12, and 24. Cases randomized to the undressed control group were assessed at weeks 4, 12, 24, 36, and 48 and at follow-up weeks 4, 12, and 24. Adverse events were managed by cure reduction or termination of study drug(s). One- step cure reduction was allowed; interferon alfa- 2b was reduced from 3 to1.5 MIU 3 times a week, and ribavirin was reduced from 1200 or 1000 to 600 mg/ day and from 800 to 400 mg/ day. Cure reduction of interferon alfa- 2b was initiated for dropped neutrophil counts ≤ 750/ mm3 or dropped platelet counts ≤,000/ mm3. endless termination of interferon alfa- 2b was needed for neutropenia ≤ 500/ mm3 or thrombocytopenia ≤,000/ mm3. For ribavirin, cure reduction was initiated for a drop in hemoglobin< 10 g/ dL and the medicine was discontinued for a drop< 8 g/ dL. Cure reduction of ribavirin was initiated for an elevation of bilirubin position to twice the entry value, whereas elevation of bilirubin position> 150 µmol/ L urged discon tinuation of ribavirin. Both medicines were discontinued if serum creatinine position was ≥ 300 µmol/L. Cases who endured rejection according to Banff criteria(Banff score, 4 – 9) discontinued interferon alfa- 2b and continued ribavirin at the same cure during treatment with antirejection remedy. Cases who endured mild rejection discontinued interferon alfa- 2b and continued ribavirin at the same cure. similar cases were renewed at a lower cure of interferon alfa- 2b handed that a liver vivisection performed 10 days latterly showed no fresh substantiation of rejection.

Efficacity End Points

The primary efficacity end point was response status, which was grounded on both serum HCV RNA quantitative PCR and change in liver histology as estimated by the METAVIR criteria at the end of treatment. The liver vivisection was consid ered bettered if the change from birth in the METAVIR exertion score was a drop of one or further and the change from birth in the METAVIR fibrosis score was nil or further, or if the change from birth in the METAVIR exertion score was either o or a drop of one or further and the change from birth in the METAVIR fibrosis score was a drop of one or further. A complete response was defined as a negative serum HCV RNA PCR and a vivisection bettered from birth as preliminarily defined. A significant response was defined as a negative PCR in the absence of worsening of liver histology or as a drop> 50 of serum HCV RNA position from birth with a vivisection im- proved from birth. Nonresponse was defined as the absence of either a complete significant response. The secondary efficacity end points were(1) the change from birth viral cargo as measured by HCV RNA at the end of treatment and at 24 weeks after treatment;(2) the change from birth in histology as assessed by the METAVIR exertion and fibrosis score at the end of treatment and at 24 weeks after treatment, independently;(3) alanine aminotransferase(ALT) values over time; and(4) the number of

rejection occurrences and the inflexibility of rejection. This study was approved by the Comite ´ de Protection de La Recherche Biome´dicale(CCPPRB) of Paris- Necker. All cases handed written informed concurrence before witnessing any protocol- related procedures

Results

Case Characteristics

Ninety- two cases were screened and 52 were randomized at 2 centers. The selection process show in Figure 1. The demographics and characteristics of the 52 randomized cases are shown in Table 1. All cases in both groups were white, and all had a first transplant. The 2 groups were analogous except for serum HCV RNA cargo, which was significantly advanced in the treated group at birth. A aggregate of 82 in the treated group and 83 in the control group were infected with genotype 1. Liver cirrhosis was present in one case in each group. utmost cases(68 in the treated group and 83 in the control group; not significant) had entered their transplant further than 2 times preliminarily. The mean detention between transplantation and study entry was4.3 times(range,0.7 –9.42 times) and4.9 times(range,1.03 –10.9 times) in the treated and control groups, independently. The mean exertion score was1.3(range, 0 – 3) and (range, 0 – 2) and the mean fibrosis score was1.7(range, 1 – 4) and1.3(range, 1 – 4) in the treated and control groups, independently(not significant). Immunosuppressive treatment was original in the 2 groups. In the treated group, 13 cases were on cyclosporine and prednisone; 5 on cyclosporine, prednisone, and azathioprine; 5 on tacrolimus and corticosteroids; 4 on tacrolimus, prednisone, and azathioprine; and one on cyclosporine monotherapy. In the control group, 9 cases were on cyclosporine and prednisone; 5 on cyclosporine, prednisone, and azathioprine; 6 on tacrolimus and corticosteroids; 3 on cyclosporine monotherapy; and one on tacrolimus monotherapy.

Safety

Adverse events with the use of interferon alfa- 2b plus ribavirin are shown in Table 2. The most constantly reported adverse events included frazzle, fever, flu- suchlike symptoms, headache, diarrhea, nausea, puking, musculoskeletal pain, myalgia, and depression. Twenty- one of 28 treated cases(75) completed 24 weeks of treatment; still, only 16(57) completed 48 weeks of treatment. pullout from the study due to adverse events passed in 12 of 28 cases(43) in the treated group versus 2 of 24(4) in the control group. The main cause for termination was anemia, which passed in 7 treated cases(25)(Table 3). habitual rejection was observed in one case(3.5) in the treated group and in none in the placebo group. One case in the control group failed from septic shock, whereas there were no deaths in the treated group.

Efficacity Results

Response to treatment according to protocol def inition. Complete response at the end of follow- up as defined by the protocol(negative serum HCV RNA and a vivisection bettered from birth) was observed in 5 of 28 cases(18) in the treated group versus none of the cases in the control group(not significant)(P 50 of serum HCV RNA position from birth with a vivisection bettered from birth) was observed in 7 of 28 cases(25) in the treated group versus none in the control group and a nonresponse in 16 of 28 cases(57) in the treated group versus 100 in the control group. Biochemical response. In the treated group, 20 cases had abnormal ALT situations in serum at the launch of treatment and 8 had situations within normal limits. In the control group, 17 cases had abnormal ALT situations in

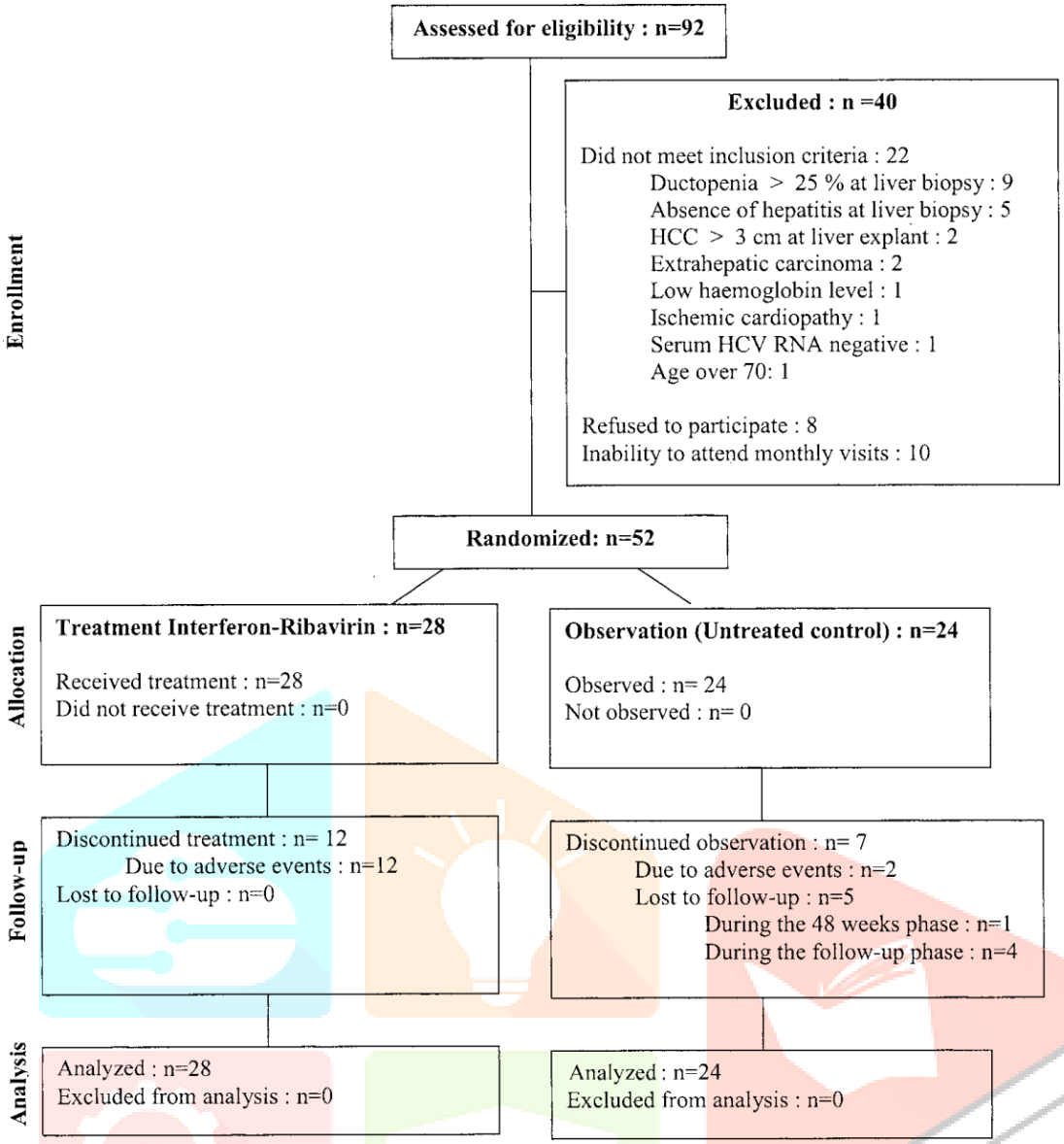

Figure 1: Flow chart of the selection process of the 2 groups of patients. HCC, hepatocellular carcinoma; ductopenia, lossof more than 25% interlobularbile ducts at screening biopsy.

serum at the launch of treatment and 7 had situations within normal limits(N). At the end of treatment, mean ALT position was0.8 N ±0.55 in the treated group versus1.6 N ±1.02 in the control group. At the end of follow- up, mean ALT position was1.65 N ±1.65 in the treated group versus1.66 N ±1.38 in the control group. Five of the 6 sustained virologic askers had normal ALT situations. Virologic response. Serum HCV RNA concurrence at colorful time points is shown in Table 4. At the end of treatment(indeed if treatment was stopped precociously), 9 of the 28 treated cases(32) were HCV RNA negative; by the end of follow- up, 6(21) had cleared HCV RNA from serum versus none in the control group(P = 0.036). Due to the low number of cases withnon-1 genotype, we weren't suitable to dissect the virologic response in relation to genotype. still, it should be emphasized that 5 of 23 cases(21) with genotype 1 had a sustained virologic response. There was a2.88 ±1.86,2.82 ±2.16, and1.38 ±2.16 mean reduction in log10 HCV RNA position at weeks 24 and 48 and at the end of follow- up, independently, compared with no change in the control group(P ≤0.0001 at each- time points and P = 0.04 at the end of follow- up)(Figure 2). Virologic response wasn't related to pretreatment viral cargo; a sustained virologic response was observed in 1 of 6 cases(16.6) with a serum viral cargo 2 million clones/ ml. There was no relation- boat between virologic response and the time between transplantation and launch of treatment. The characteristics of the 6 cases with a sustained virologic response are shown in Table 5. All but one had a detention of further than 4 times post transplantation before addition in the study; 5 were infected with genotype 1b, 5 had a serum viral cargo at the launch of the treatment> 2 million clones/ mL, and none had a degree of fibrosis> 2.

Treated cases who showed a loss of HCV RNA at week 24 had a lesser mean drop in HCV RNA at all.

Table 1. Patient Characteristics

aracteristics	Treatedgroup	Control group	*P*
n	28	24	
Sex (M/F)	18/10	18/6	
Age (*yr*)	56 ± 8	58 ± 6	NS
Interval between transplantation and study inclusion (mo)	54 ± 39	57 ± 34	NS
ALT level at inclusion (× normal)	1.9 ± 1.3	1.7 ± 0.9	NS
Presence of cirrhosi (%)	1 (3.5)	1 (4.1)	
Weight > 75 kg	46%	50%	
Genotype			
1 (%)	23 (82)	20 (83)	NS
2	0	2	
3	1	2	
4	1	0	
Nontypeable	1	0	
Missing	2	0	
HCV RNA level a screening (*million copies/mL*)	14.3 6.1	9.4 15.1	NS
HCV RNA at inclusio (*million copies/mL*)	19 ± 20	8.5 ±0.02 14.6 8	
HCV RNA >2 millio copies/mL	22 (78.5%)	14 (58.3%)	0.06

Table **3.** Reasons for Withdrawal from the Study

Causes	Treated group (= 28)	Control grou (n = 24)	*P*
Insomnia	1	0	NS
Depression	1	0	NS
Irritability	2	0	NS
Death	0	1*a*	NS
Progression of fibrosis	0	1	NS
Lost to follow-up	0	5	NS

*a*Died from septi shock.

Table 4. Loss of Serum HCV RNA at Various Time Points

Tre ated gro up (%)	Week 4	3/28 (10.7)	0	
	Week 12	5/28 (17.9)	0	
	Week 24	8/28 (28.6)	0	
	Week 48	7/28 (25)	0	0.016*a*
	End of treatment	9/28 (32)	—	
	Week 24 follow up	6/28 (21.4)	0	0.036*a*

	Control group	*P*

*a*Fisher exac test.

Table 2. Main Adverse Events in the Treated and ControlGroups

Type of event	Treated group		Control group	
	All (%)	Severe (%)	All (%)	Severe
All	28 (100)	12 (43)	21 (88)	3 (13
Hypotension	2 (7)	2 (7)	0	0
Dry mouth	2 (7)	1 (4)	0	0
Tiredness	27 (96)	4 (14)	8 (33)	1 (4)
Fever	8 (29)	0	1 (4)	1 (4)
Flu-like symptoms	7 (25)	1 (4)	0	0
Headache	9 (32)	1 (4)	0	0
Weight loss	3 (11)	0	2 (8)	0
Abdominal pain	5 (18)	0	3 (13)	0
Anorexia	3 (11)	0	0	0
Diarrhea	7 (25)	0	0	0
Nausea	8 (29)	0	1 (4)	0
Vomiting	7 (25)	0	2	0
Diabetes	2 (7)	0	1 (4)	0
Hyperuricemia	3 (11)	0	1 (4)	0
Arthralgia	6 (21)	1 (4)	1 (4)	0
Myalgia	7 (25)	0	1 (4)	0
Thrombocytopenia	2 (7)	0	0	0
Anemia	19 (68)	5 (18)	1 (4)	0
Neutropenia	6 (21)	0	0	0
Psychiatric disorders	12 (43)	3 (11)	1 (4)	0
Depression	7 (25)	1 (4)	1 (4)	0
Insomnia	5 (18)	1 (4)	0	0
Irritability	3 (11)	1 (4)	0 (4)	0
Nervousness	2 (7)	0	0	0

Histologic results: An increased proportion of cases treated with interferon alfa- 2b plus ribavirin showed an enhancement in METAVIR exertion scores at the end of treatment compared with the control group(54vs. 21). still, at the end of the follow-up period, the difference was undetectable(25vs. 21). Although enhancement in fibrosis METAVIR score was lesser at the end of treatment(14) and the end of follow- up(14) in the treated group compared with the control group(4), the difference wasn't significant.

Discussion

This study is the first randomized, controlled study of combination remedy with interferon plus riba virin in liver transplant donors infected with HCV. It shows that combination remedy with interferon plus ribavirin is doable in liver transplant donors and that 12 months of treatment was superior to standard care plus observation in producing a sustained virologic re sponse in 21 of treated versus 0 of control cases. still, forbearance was an important limiting factor because 43 of treated cases had to discontinue study drug, substantially because of anemia due to ribavirin. HCV rush on the graft is a major problem after liver transplantation. nearly all cases will develop rush, and roughly 70 – 80 will develop mild to severe habitual hepatitis. The rate of development of cirrhosis on the graft varies between 8%

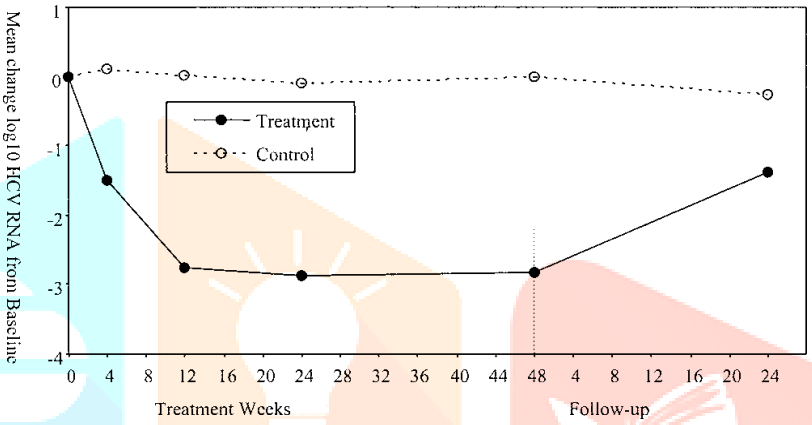

Figure 2. Mean changes in serum HCV RNA from birth expressed in log10 for cases treated with interferon alfa- 2b plus ribavirin as well as control cases. The mean birth value of HCV RNA in the treated and control groups was6.81 ±1.07 and6.38 ±0.81, independently. The mean drop in HCV RNA was —2.76 ±1.58, —2.88 ±1.86; —2.82 ±2.16, and —1.38 ±2.16, independently, at weeks 12, 24, and 48 and at the end of follow- up. There was no change in mean HCV RNA situations in the control group(0.02, —0.11,0.00, and —0.25, independently, at weeks 12, 24, and 48 and at the end of follow- up). The mean drop in log10 HCV RNA position was significant at all time points(P< 0.0001 at all-time points and *P* =0.04 at the end of follow-up).

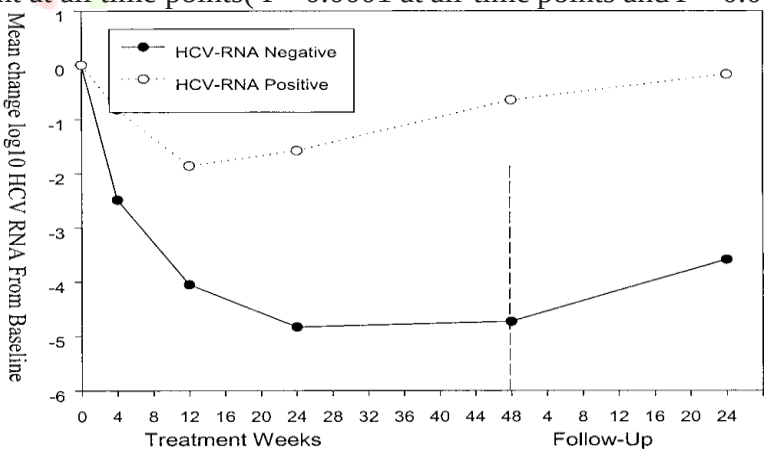

Figure 3. Mean changes in HCV RNA from baseline among patients treated with interferon alfa-2b plus ribavirin who were HCV RNA negative.

and 28 at 5 times and was lately reported to be advanced in cases who passed transplantation in recent times. In a European multicenter study of 652 cases, the rate of cirrhosis was 10 at 5 times with an anticipated rate of 24 at 8 times. Cirrhosis really becomes further frequent with posttransplant duration and has a injurious impact on long-term case survival. To avoid similar negative issues, it seems important to help or treat HCV infection on the graft. Prevention of HCV infection after transplantation is delicate and, unlike the situation with forestallment of hepatitis B contagion after transplantation, there are noanti-HCV immunoglobulins. Precautionary antiviral treatment incontinently after transplantation has infrequently been tried with interferon alone or with combination interferon plus ribavirin, and this approach graces farther disquisition. Ribavirin alone achieves normalization of liver enzyme situations in utmost cases but without any virologic response. Interferon alfa alone has been used after liver transplantation for the treatment of HCV rush, but all studies have shown a poor antiviral effect with a sustained virologic response rate< 5 and a implicit threat of acute or habitual rejection. In a former case- controlled study, we observed the circumstance of habitual rejection in 5 of 14

Table 5. Characteristics of the 6 Patients With Sustained Virologic Response

	Patient					
	1	2	3	4	5	6
Sex	M	M	M	M	M	M
Age (*yr*)	62	61	60	60	64	51
Interval between live transplantation and treatment (*yr*)	4.1	4.5	8.3	5.0	6.0	0.7
Genotype	1b	1b	Unknown	1b	1b	1b
Histology (METAVIR)						
Screening	A2F1	A1F1	A0F1	A1F1	A2F1	A1F2
Wk 24 follow-up	A1F1	A1F1	A1F1	A1F1	A0F1	A1F2
HCV RNA level (*copies/mL*)						
Screening	19,000,000	48,000,000	4,200,000	4,600,000	880,000	11,000,000
Study entry	33,000,000	72,000,000	2,800,000	4,300,000	1,200,000	27,000,000
Wk 4	130,000	2,700,000	<100	160,000	4200	Unknown
Wk 12	660	<100	<100	16,000	<100	<100
Wk 24	<100	<100	<100	<100	<100	<100
Wk 48	<100	<100	<100	<100	<100	<100
Wk 24 follow-up	<100	<100	<100	<100	<100	<100
ALT (× normal value) (normal value, 1)						
Study entry	1.4	1.05	0.93	2.23	3.7	4.61
Wk 24 follow-up	0.44	1.84	0.91	0.23	0.37	0.47

This is the first randomized study of cases with intermittent habitual hepatitis C on the graft entering a tiviral combination treatment with interferon plus riba- virin in comparison with no treatment. Our end in keeping a control group without treatment was to show both salutary and injurious goods of antiviral treatment. In particular, there was a need to validate whether such an antiviral combination would be well permitted by transplant donors, especially in terms of the threat of rejection and the development of hematologic forbearance. A farther consideration is that not all liver transplant donors with HCV reinfection need treatment, because 20 – 30 will have a benign course. For all these reasons, we named a group of transplant donors with intermittent habitual hepatitis C who had been followed up for a minimum of 6 months after transplantation to avoid the addition of cases with acute hepatitisC. Cases with histologic features of rejection were barred from the study. We designed a study with the stylish available treatment against hepatitis C, which was, at time of the design of the study, com- bination remedy with interferon alfa- 2b(3 MIU 3 times a week) + 1000 – 1200 mg per day ribavirin. The 12- month duration of treatment was choose to increase the sustained response rate. To help any rejection occasion in the treated group and to descry any histologic progression of hepatitis in the control group, a liver vivisection was performed at entry, at 24 and 48 weeks, and at 24 weeks after end of treatment in both groups. This study showed that combination treatment was fairly well permitted; 16 of the 28 cases continued treatment until the end of the 48- week study period. still, it was necessary to withdraw 12 treated cases from the study compared

with only 4 in the control group. The main reason for termination of treatment was anemia. This well-known secondary effect of ribavirin was frequent & more severe in this transplant population than in immunocompetent cases. This may be due to the disabled renal function of transplant donors entering long- term nephrotoxic immunosuppressive medicines and to an interferon- convinced bone gist repression. Indeed, our primary experience suggested a better forbearance of ribavirin mono- remedy.9 In retrospection, the original lozenge(1000 – 1200 mg) of ribavirin sounded too high. In the design of unborn trials, the lozenge of ribavirin should be acclimated to the weight and renal concurrence of the cases.

In this study, there was no case of acute rejection and one case of habitual rejection. In this ultimate case, there was a exposure of some interlobular corrosiveness tubes and treat ment was stopped. The extent to which this can be imputed to interferon isn't certain, but it can not be ruled out. Overall, the rate of habitual rejection was remarkably low in this study. It has been suggested that the addition of ribavirin may have an immunomodula tory effect and may drop the threat of rejection due to interferon.9 This needs to be verified because our cases were named on a base of the absence of histologic features of rejection. Other side goods observed were those generally seen in nontransplant cases, similar as depression, fatigue, anxiety, and perversity. There was one death due to sepsis in control group & no deaths in the treated group. One case in the control group had to be withdrawn from the study because of fibrosis progression.

The most remarkable result of this study was an end- of- treatment virologic response rate of 32 and a sustained serum HCV RNA concurrence rate of 21. A relationship between viral factors similar as viral cargo, genotype, and response to treatment couldn't be estaba lished. This may be due to the small number of cases included and the fact that 83 of the treated cases were infected with genotype 1b. It should be noticed that among the 6 sustained askers, 6 were infected with genotype 1b and 5 had a viral cargo at the launch of treatment> 2 million clones/ mL; both factors are generally considered predictors of a low virologic re- sponse rate. Five of the 6 responding cases had histo sense mild hepatitis, and 5 had a stage 1 fibrosis at the launch of treatment. Only one of the askers had a rapid-fire severe hepatitis with a stage 2 fibrosis lower than 1 time after transplantation. There was an overall significant virologic response during treatment with a mean reduction from birth of2.88 log10 HCV RNA in the treated group versus no change in the control group at weeks 12 and 48(Figure 2).

The dynamics of this virologic response(Figure 3) showed that all cases who responded at week 24 had a sharp decline in HCV RNA after the launch of treatment. Among the cases with a sustained virologic response, 2 were still HCV RNA positive at 12 weeks and all were HCV RNA negative at week 24. The impact of viral response on histology is delicate to assess. There was no major difference in the exertion and fibrosis stage before treatment and at the end of follow- up. It's possible that an effect on histology will be seen with a longer follow- up. In addition, the addition of cases with low fibro- sis scores may have rendered delicate the analysis of fibrosis retrogression. Our results are in line with recent studies on the combined use of interferon plus ribavirin in liver transplant donors, which show a virologic response rate of 8 – 33. All these studies showed a advanced rate of treatment termination than in non- transplant populations and substantially due to poor hematologic forbearance. The effect of lower tablets of interferon and ribavirin as well as the use of erythropoietin and granulocyte- stimulating factors should be explored. Erythropoietin was inadequate to correct anemia in a recent study. The salutary effect of 6 versus 12 months of treatment on the rate of sustained virologic response wasn't shown in a recent study and treat- ment duration needs to be explored further in larger series of cases including infections with genotypes 1 andnon-1. The ideal timing for starting antiviral treatment can not be derived from our study and also needs to be further explored. A advanced virologic response rate with pegylated interferon alfa than with interferon alfa has lately been shown in the nontransplant population, particularly in cases with genotype 1 infections. This salutary virologic effect of pegylated interferon can not be decided to the transplant population without farther studies because it might be canceled by a advanced threat of hematologic and contagious complications in the transplant donors, in whom interferon is likely to have a longer half- life and predominant renal concurrence.

In conclusion, this study shows for the first time that

months of antiviral combination remedy for rush of HCV after liver transplantation may achieve a 21 sustained virologic response rate and is significantly superior to no treatment. In addition, the study shows that side goods are similar with those seen in non- transplant cases piecemeal from hemolytic ane ia, which was more frequent and more severe among these posttransplant cases. The circumstance of anemia may be reduced in the future by conforming the original lozenge of ribavirin to the case' s weight and renal function, and its inflexibility may be bettered by treatment with erythropoietin. An important finding is that the theoretical threat of graft rejection by treatment with interferon alfa- 2b plus ribavirin has not been substantiated in this study. Because utmost treatment discontinua tions passed after the 6- month course, the benefit of continuing treatment with interferon beyond 6 months alongside conservation ribavirin alone can be questioned. This study is the starting point for the development of unborn antiviral strategies to treat rush of HCV after liver transplantation.

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