ORIGINAL ARTICLE

Ribavirin for Chronic Hepatitis E Virus Infection in Transplant Recipients

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ABSTRACT

BACKGROUND

There is no established therapy for hepatitis E virus (HEV) infection. The aim of this retrospective, multicenter case series was to assess the effects of ribavirin as monotherapy for solid-organ transplant recipients with prolonged HEV viremia.

METHODS

We examined the records of 59 patients who had received a solid-organ transplant (37 kidney-transplant recipients, 10 liver-transplant recipients, 5 heart-transplant recipients, 5 kidney and pancreas–transplant recipients, and 2 lung-transplant recipients). Ribavirin therapy was initiated a median of 9 months (range, 1 to 82) after the diagnosis of HEV infection at a median dose of 600 mg per day (range, 29 to 1200), which was equivalent to 8.1 mg per kilogram of body weight per day (range, 0.6 to 16.3). Patients received ribavirin for a median of 3 months (range, 1 to 18); 66% of the patients received ribavirin for 3 months or less.

RESULTS

All the patients had HEV viremia when ribavirin was initiated (all 54 in whom genotyping was performed had HEV genotype 3). At the end of therapy, HEV clearance was observed in 95% of the patients. A recurrence of HEV replication occurred in 10 patients after ribavirin was stopped. A sustained virologic response, defined as an undetectable serum HEV RNA level at least 6 months after cessation of ribavirin therapy, occurred in 46 of the 59 patients (78%). A sustained virologic response was also observed in 4 patients who had a recurrence and were re-treated for a longer period. A higher lymphocyte count when ribavirin therapy was initiated was associated with a greater likelihood of a sustained virologic response. Anemia was the main identified side effect and required a reduction in ribavirin dose in 29% of the patients, the use of erythropoietin in 54%, and blood transfusions in 12%.

CONCLUSIONS

This retrospective, multicenter study showed that ribavirin as monotherapy may be effective in the treatment of chronic HEV infection; a 3-month course seemed to be an appropriate duration of therapy for most patients.

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N Engl J Med 2014;370:1111-20.
DOI: 10.1056/NEJMoa1215246

Hepatitis e virus (HEV) genotype 3 causes self-limiting infection in non-immunocompromised patients.[1,2] However, it can lead to chronic hepatitis and cirrhosis in patients who have received solid-organ transplants,[3] patients with human immunodeficiency virus infection,[4] and patients with hematologic cancers who are receiving chemotherapy.[5] In a large cohort of solid-organ transplant recipients, HEV infection evolved to chronic infection in approximately 66% of the patients and to cirrhosis in 10%.[6] Furthermore, several HEV-induced extrahepatic manifestations (e.g., neurologic symptoms and kidney injuries) have been reported in transplant recipients who are infected with HEV.[7-9]

To date, there is no established therapy for HEV infection. A reduction in immunosuppressive therapy, mainly immunosuppressants that target T cells, has resulted in HEV clearance in nearly 30% of solid-organ transplant recipients with chronic hepatitis.[6-10] Small case series and case reports in this population have shown that a short course of pegylated interferon or ribavirin as monotherapy can effectively treat HEV infection.[11-14] Here we report a combined case series from several transplantation centers in France, involving solid-organ transplant recipients infected with HEV who were treated with ribavirin alone. The aim of our study was to assess the efficacy and safety of ribavirin as monotherapy for HEV infection.

Methods

Participating Centers and Study Oversight

The 23 regions in France that have a solid-organ transplantation program were invited to participate in this retrospective case series; 13 centers agreed to participate in the study. Data on all cases of autochthonous HEV infection in solid-organ transplant recipients who had been treated with ribavirin alone between September 10, 2009, and June 27, 2012 (59 patients), were collected from the 13 participating centers: Toulouse University Hospital, Toulouse (22 patients); Montpellier University Hospital, Montpellier (9); Cochin University Hospital, Paris (6); Foch Hospital, Suresnes (5); Edouard Herriot University Hospital, Lyon (4); Lyon Nord Croix-Rousse Hospital, Lyon (3); Paul Brousse University Hospital, Villejuif (3); Tours University Hospital, Tours (2); Bordeaux University Hospital, Bordeaux (1); Lille University Hospital, Lille (1); Dijon University Hospital, Dijon (1); Nantes University Hospital, Nantes (1); and Pitié–Salpêtrière University Hospital, Paris (1). During the study period, all patients at participating centers who had increased liver-enzyme levels that were attributable to persistent HEV replication were treated with ribavirin monotherapy. The study was approved by the institutional review boards at Toulouse and Cochin University Hospitals, and all the patients gave written informed consent to participate in the study. At each center, an investigator collected patients' data from medical records. All the authors vouch for the completeness and accuracy of the data presented.

Virologic Assessments

Solid-organ transplant recipients in whom HEV infection was diagnosed by means of detection of HEV RNA in the serum had a prospective follow-up that determined the duration of HEV infection. For some patients, the time of infection was determined with the use of frozen serum. All samples were analyzed at the French reference center for HEV in Toulouse. HEV RNA was detected and quantified with the use of a polymerase-chain-reaction test for HEV genotype 3 that was validated and accredited according to the International Organization for Standardization 15189 standards, as described previously.[15] The limit of detection for HEV RNA was 100 copies per milliliter. A sustained virologic response was defined as an undetectable level of HEV RNA in the serum at least 6 months after completion of ribavirin therapy. Levels of anti-HEV IgM and IgG antibodies were assessed with the use of commercially available kits: the EIAgen HEV IgG and IgM kits (Adaltis) (before 2012) and the Wantai HEV IgG and IgM enzyme-linked immunosorbent assay (Beijing Wantai Biological Pharmacy Enterprise) (during 2012).

Statistical Analysis

Proportions were compared with the use of the chi-square test or Fisher's exact test. Quantitative variables were compared with the use of the nonparametric Friedman test for serial measurements and either Student's t-test or the Wilcoxon test. Independent factors associated with a sustained virologic response were assessed with the use of a stepwise multivariate logistic-regression model that included variables with a univariate P value of less than 0.05; the analysis was performed with the use of StatView software (SAS

Institute). In this analysis, patients with a sustained virologic response (as defined above) were compared with those without a sustained virologic response. A P value of less than 0.05 was considered to indicate statistical significance. All P values are two-sided.

RESULTS

RIBAVIRIN THERAPY

The median time between the diagnosis of HEV infection and the initiation of ribavirin therapy was 9 months (range, 1 to 82) (Table 1). At the time that ribavirin therapy was initiated, 34 patients had had persistently positive tests for serum HEV RNA for at least 6 months, 20 patients had had viremia for 3 to less than 6 months, and 5 patients had been infected for less than 3 months.

Ribavirin therapy was initiated at a median dose of 600 mg per day (range, 29 to 1200), which was equivalent to 8.1 mg per kilogram of body weight per day (range, 0.6 to 16.3). Initial ribavirin doses were adjusted on the basis of the estimated glomerular filtration rate (GFR), as described previously.[16] The adjusted doses were as follows: 200 mg per week (1 patient), 400 mg per week (1 patient), 600 mg per week (2 patients), 200 mg every other day (1 patient), 200 mg per day (4 patients), 300 mg per day (1 patient), 400 mg per day (10 patients), 600 mg per day (17 patients), 800 mg per day (17 patients), 1000 mg per day (4 patients), and 1200 mg per day (1 patient). Ribavirin was administered for a median of 3 months (range, 1 to 18); the durations of therapy were as follows: 1 month (3 patients), 3 months (36 patients), 4 months (1 patient), 4.5 months (1 patient), 5 months (1 patient), 6 months (12 patients), 10 months (2 patients), 11 months (1 patient), 15 months (1 patient), and 18 months (1 patient). Hence, 61% of the patients received ribavirin for 3 months, and 66% received it for 3 months or less. During the time the patients were receiving ribavirin therapy, immunosuppressive medications were not discontinued and their doses were not changed substantially except in 5 patients who discontinued mycophenolic acid after undergoing a blood transfusion for severe anemia.

Although kidney function did not change appreciably during therapy, the ribavirin dose was decreased in 17 patients (29%) because of anemia and was increased in 4 other patients (7%) during treatment. Overall, median ribavirin doses were 600 mg per day at the initiation of therapy and at month 1 and 400 mg per day at month 2 and at the end of therapy (range, 29 to 1200 at all time points). Ribavirin was temporarily stopped in 2 patients because of severe anemia; it was discontinued for 10 days in a patient with a hemoglobin level of 7.0 g per deciliter and for 15 days in a patient with a hemoglobin level of 7.5 g per deciliter.

VIROLOGIC RESPONSE

All the patients had HEV viremia when ribavirin was initiated. One patient was lost to follow-up within the first month after the initiation of ribavirin, and another patient was withdrawn from ribavirin at month 1 for psychiatric reasons. At month 1, HEV RNA levels were assessed in 50 patients, and the level was undetectable in 32 patients (64%). At month 3 and at the end of therapy, 56 of the 57 patients who were followed had HEV clearance (Fig. 1). The sole patient who still had viremia at the end of therapy had a severe drop in hemoglobin level during therapy and required a 10-day interruption in ribavirin therapy and a blood transfusion. His GFR, estimated with the use of the Modification of Diet in Renal Disease equation at the initiation of therapy, was 50 ml per minute per 1.73 m^2 of body-surface area. His initial dose of ribavirin was 800 mg per day (13 mg per kilogram per day); at month 2, after the short interruption in ribavirin therapy, the dose was decreased to 400 mg per day.

Among the 56 patients who had no detectable virus by the end of therapy, a recurrence of HEV replication occurred in 10 patients (Fig. 1). Hence, a sustained virologic response was observed in 46 of the 59 patients (78%) (Fig. 2). At the most recent follow-up, at a median of 25 months after the end of therapy (range, 6 to 42), these 46 patients still did not have viremia. The rate of sustained virologic response did not differ significantly between the 39 patients who had received ribavirin therapy for 3 months or less and the 20 patients who had received it for more than 3 months (74% and 85%, respectively) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Among the 18 patients who had viremia after 1 month of therapy, the rate of sustained virologic response was 50% among the 12 patients who received ribavirin therapy for 3 months or less and 83% among the 6 patients who received the therapy for more than 3 months (P=0.32).

Of the 10 patients who had a recurrence, 6 patients were re-treated. Five of these patients, who had initially been treated for 3 months, were re-treated for 6 months. Four of them had a sustained virologic response, whereas the fifth patient had clearance of the virus by 3 months after the end of therapy. The sixth patient, who had initially been treated for 4.5 months, was re-treated for 12 months. He had clearance of the virus and is still receiving therapy. Finally, a patient with a partial response was re-treated at a dose of 400 mg daily after a washout period of 8 months. He had clearance of the virus 15 months after the initiation of re-treatment, and with maintenance of therapy, the serum HEV RNA level was still undetectable at 25 months after the initiation of re-treatment.

BIOCHEMICAL RESPONSE

Liver-enzyme levels decreased in all the patients during and after ribavirin therapy (Table S1 in the Supplementary Appendix). At 6 months after the end of therapy, levels of alanine aminotransferase and aspartate aminotransferase were within the normal ranges in all patients, except in two liver-transplant recipients. At the same time point, levels of γ-glutamyltransferase were above the normal range in three liver-transplant recipients, two kidney-transplant recipients, and one heart-transplant recipient.

Table 1. Demographic and Clinical Characteristics of the 59 Patients.*

Variable	Value
Age — yr	
Median	51
Range	25–74
Sex — no. (%)	
Male	47 (80)
Female	12 (20)
Type of organ transplant — no. (%)	
Kidney	37 (63)
Liver	10 (17)
Heart	5 (8)
Kidney and pancreas	5 (8)
Lung	2 (3)
History of acute rejection — no. (%)	19 (32)
Immunosuppressive therapy at the initiation of ribavirin — no. (%)	
Calcineurin inhibitor	47 (80)
Antimetabolite	45 (76)
Glucocorticoid	44 (75)
Tacrolimus	42 (71)
mTOR inhibitor	13 (22)
Cyclosporine	5 (8)
Serum creatinine at the initiation of ribavirin — μmol/liter†	149±70
Estimated GFR at the initiation of ribavirin — ml/min/1.73 m^2‡	52±21
Lymphocyte count at the initiation of ribavirin — cells/mm^3	1379±912
Hemoglobin level at the initiation of ribavirin — g/dl	
Median	13.4
Range	8.7–16.7
Use of recombinant erythropoietin at the initiation of ribavirin — no. (%)	15 (25)
Platelet count at the initiation of ribavirin — cells/mm^3	183,000±72,000
Prothrombin index — %	
Median	80
Range	65–100

Table 1. (Continued.)

Variable	Value
Albumin at the initiation of ribavirin — g/liter	39±5
Positive test for anti-HEV IgG antibodies at the initiation of ribavirin — no./total no. (%)	38/50 (76)
Positive test for anti-HEV IgM antibodies at the initiation of ribavirin — no./total no. (%)	55/57 (96)
Positive test for serum HEV RNA at the initiation of ribavirin — no. (%)	59 (100)
HEV genotype 3 — no. (%)§	54 (92)
Interval between transplantation and initiation of ribavirin — mo	
Median	56
Range	7–293
Interval between diagnosis of HEV infection and initiation of ribavirin — mo	
Median	9
Range	1–82

* Plus–minus values are means ±SD. HEV denotes hepatitis E virus, and mTOR mammalian target of rapamycin.
† To convert values for creatinine to milligrams per deciliter, divide by 88.4.
‡ The glomerular filtration rate (GFR) was estimated with the use of the Modification of Diet in Renal Disease equation.
§ HEV genotyping was not performed in five patients.

SAFETY OF RIBAVIRIN THERAPY

Before ribavirin therapy, the median hemoglobin level was 13.4 g per deciliter (range, 8.7 to 16.7), and 15 patients (25%) were receiving recombinant erythropoietin. During therapy, hemoglobin levels decreased significantly, to a median of 11.6 g per deciliter (range, 7.2 to 16.9) by the end of therapy (P<0.001) (Fig. 3). Overall, 32 patients (54%) received recombinant erythropoietin on a transient or regular basis during ribavirin therapy, and 24 patients (41%) received recombinant erythropoietin at the end of therapy. Seven patients (12%) required a blood transfusion; 2 of these patients were concomitantly receiving chemotherapy for cancer, and 1 of the 2 patients had a sustained virologic response. No episodes of acute rejection were observed during ribavirin therapy. Two patients who had a recurrence of HEV replication died during the study period: 1 died from cardiovascular disease 22 months after the end of ribavirin therapy, and 1 died from lung cancer 5 months after the end of ribavirin therapy.

FACTORS ASSOCIATED WITH A SUSTAINED VIROLOGIC RESPONSE

We analyzed a number of variables that could potentially influence the rate of sustained virologic response (Table 2, and Table S2 in the Supplementary Appendix). Two variables were included in a multivariate analysis: total lymphocyte count at the initiation of ribavirin therapy and a positive test for HEV RNA at month 1. Given the limited power of this analysis, the only independent predictive factor associated with a sustained virologic response was a higher lymphocyte count at the initiation of ribavirin therapy.

DISCUSSION

When HEV genotype 3 infection occurs in solid-organ transplant recipients, it can evolve to cirrhosis and may require liver transplantation.[6] This retransplantation in patients with viremia in the liver may reinduce chronic HEV infection.[17] In contrast, no HEV reactivation has been observed after kidney retransplantation in patients who had clearance of the virus.[18] HEV-associated neurologic and renal manifestations may completely or partially resolve after HEV clearance.[7,9] Hence, in patients chronically infected with HEV, viral clearance should be a goal, to avoid potential progression of liver fibrosis and extrahepatic manifestations. The aim of our retrospective case series was to assess the effects of ribavirin as monotherapy for HEV infection. Our study has three main findings: first-line ribavirin therapy was associated with a sustained virologic response in 78% of the patients; among patients who had a recurrence and completed a second and prolonged course of ribavirin, a sustained virologic response could be achieved in most patients; and a higher lymphocyte count appeared to be associated with a sustained virologic response after ribavirin therapy.

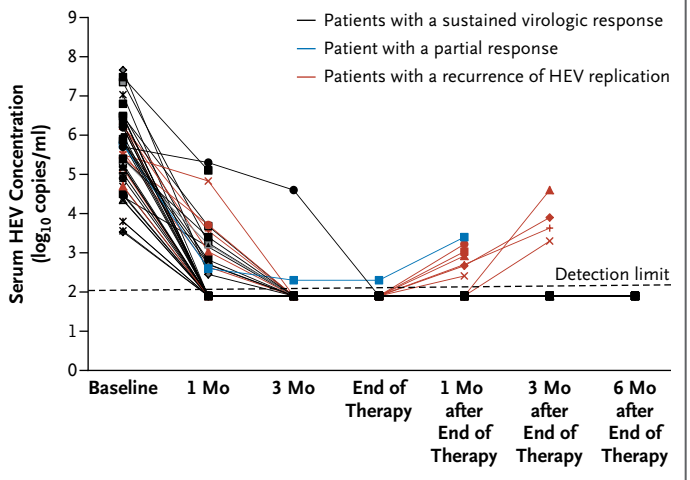


Figure 1. Hepatitis E Virus (HEV) Concentration during Ribavirin Therapy.

Data from in vivo and in vitro studies suggest that HEV infection can evolve to chronic hepatitis in patients who are immunosuppressed.[3,6,19] In a previous study, we found that a reduction in immunosuppression led to HEV clearance in only one third of patients with chronic HEV infection.[6] Hence, specific therapies were required for the remaining two thirds of the patients.

Pegylated interferon, which has been successfully used in small case series,[11,12,20-22] is not recommended for kidney-transplant and heart-transplant recipients because of concern about acute rejection[23]; thus, ribavirin has been administered as monotherapy in efforts to treat chronic HEV infection. Encouraging results have been obtained in small case series.[13,14,24-32] The current case series included a larger number of patients who were given ribavirin to treat HEV infection. When ribavirin therapy was initiated,

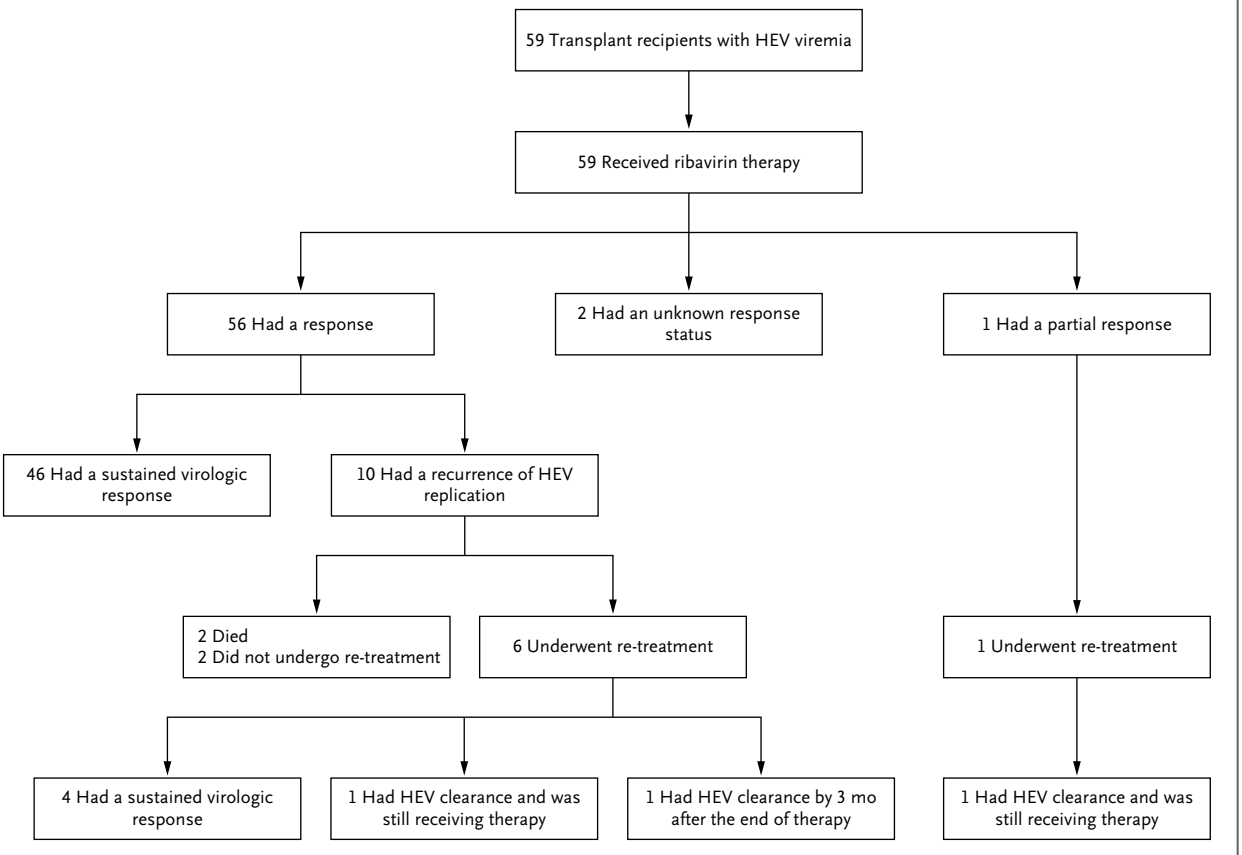
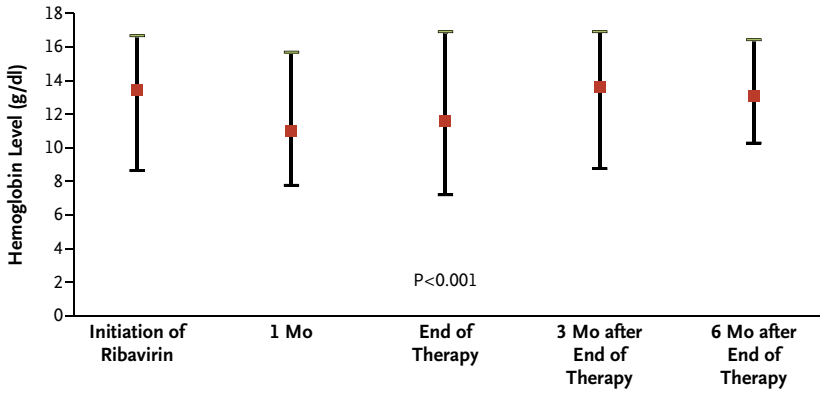


Figure 2. Outcomes of Ribavirin Therapy in Solid-Organ Transplant Recipients with HEV Infection.

The response status of two patients was unknown: one patient was lost to follow-up, and the other was withdrawn from ribavirin at 1 month for psychiatric reasons. Two patients who had a recurrence of HEV replication died during the study period — one from cardiovascular disease 22 months after the end of ribavirin therapy, and the other from lung cancer 5 months after the end of therapy.



Use of rEPO (% of patients)	25	37	41	12	12
Dose of rEPO (units)					
Median	5000	10,000	16,000	5500	4500
Range	1500–20,000	1500–40,000	1500–60,000	1500–20,000	1500–16,000
Dose of Ribavirin (mg/day)					
Median	600	600	400		
Range	29–1200	29–1200	29–1200		

Figure 3. Hemoglobin Level and Erythropoietin Use before, during, and after Ribavirin Therapy.

The P value is for the comparison between initiation of ribavirin and end of therapy. The I bars represent the ranges (minimum and maximum). The term rEPO denotes recombinant erythropoietin.

34 patients had had persistently positive tests for HEV for at least 6 months, 20 patients had had viremia for 3 to less than 6 months, and 5 patients had been infected for less than 3 months. It has been observed that among organ-transplant recipients with HEV infection, spontaneous clearance of HEV between 3 and 6 months after an acute infection is uncommon: this suggests that HEV infection can be considered to be chronic when HEV replication persists for more than 3 months.[33] In the current study, 5 patients (8%) were treated after having been infected with HEV for less than 3 months. Of these, 1 had concomitant HEV-associated neurologic symptoms. However, we cannot exclude the possibility that some of these 5 patients may have had spontaneous clearance if ribavirin had not been initiated.

In our case series, ribavirin was administered for a median of 3 months (range, 1 to 18); 61% of the patients received 3 months of therapy. The rate of virologic response at the end of therapy was 95%. Only one patient still had viremia at the end of therapy: he was re-treated with the same daily dose after a period without medication. He had viral clearance at 15 months after the initiation of re-treatment, and with maintenance of therapy, the serum HEV RNA level was still undetectable at the most recent follow-up. It is unknown whether this delayed virologic response is related to nonadherence to the medication regimen, to ribavirin malabsorption, or to viral factors. Unfortunately, ribavirin levels were not assessed in this patient.

The overall rate of sustained virologic response was 78% (46 of 59 patients). Six of the 10 patients who had a recurrence were re-treated. Four of these patients, who completed a second and prolonged course of ribavirin, then had a sustained virologic response. Hence, in our study, 50 of the 59 patients (85%) had clearance of HEV viremia. A higher lymphocyte count was the only identified independent factor that was predictive of a sustained virologic response. This finding is consistent with previous findings that suggested that HEV replication persists in immunosuppressed patients.[6]

The rate of sustained virologic response was higher among patients who had viral clearance at 1 month after the initiation of ribavirin than among those who still had viremia at that time (91% [29 of 32 patients] vs. 61% [11 of 18 patients]) (Table 2). In addition, among patients who had viremia at 1 month after the initiation of ribavirin, the rate of sustained virologic response tended to be higher if they received more than 3 months

of ribavirin therapy than if they received the therapy for 3 months or less (83% vs. 50%). Nevertheless, the overall rate of sustained virologic response did not differ significantly between patients who received ribavirin for 3 months or less and those who received it for more than 3 months. Hence, our data suggest that 3 months may be an appropriate duration of ribavirin therapy in HEV-infected patients. In patients with persistent replication at 1 month after ribavirin therapy is initiated and in patients with a recurrence, a longer period of therapy may be needed. With this strategy, the majority of patients will not receive ribavirin — and therefore will not have ribavirin-induced side effects — for more than 3 months. Indeed, as expected, anemia was the main observed side effect. Two patients required a transient interruption of ribavirin therapy; 54% of patients required recombinant erythropoietin, at relatively high doses, during ribavirin therapy; and 12% of patients required a blood transfusion. Hence, ribavirin doses should be adapted to kidney function,[16] and the hemoglobin level should be monitored closely.

The mechanisms by which ribavirin achieves HEV clearance are unknown. Ribavirin (1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide), a guanosine analogue, inhibits the replication of a wide range of RNA and DNA viruses, including those in the Flaviviridae family.[34] No data are currently available regarding the effect of ribavirin on HEV replication. Ribavirin also modulates the immune response to hepatitis C virus.[35] Ribavirin can reduce lymphocyte proliferation in vitro[36] and can reduce virally induced macrophage production of proinflammatory cytokines, including tumor necrosis factor and interleukin-1,[37] and it diminishes cytokine production by type 2 helper T cells while preserving cytokine production by type 1 helper T cells.[37,38] Suneetha et al.

Table 2. Analysis of Potential Factors Predictive of a Sustained Virologic Response.*

Variable	Patients with Sustained Virologic Response (N=46)	Patients without Sustained Virologic Response (N=13)	P Value
Liver-transplant recipient — no. (%)	8 (17)	2 (15)	1.00
Aspartate aminotransferase level at the initiation of ribavirin — IU/liter			
Median	63	85	0.93
Range	21–1263	41–480	
Alanine aminotransferase level at the initiation of ribavirin — IU/liter			
Median	104	105	0.34
Range	10–1506	41–225	
γ-Glutamyltransferase level at the initiation of ribavirin — IU/liter			
Median	125	163	0.19
Range	24–914	60–1015	
Hemoglobin level at the initiation of ribavirin — g/dl			
Median	13.4	13.6	0.91
Range	8.7–16.4	11.0–16.7	
Lymphocyte count at the initiation of ribavirin — cells/mm^3			
Median	1399	748	0.02
Range	178–6000	600–1540	
Interval between transplantation and initiation of ribavirin — mo			
Median	59	44	0.09
Range	7–293	12–120	
Interval between diagnosis of HEV infection and initiation of ribavirin — mo			
Median	9	9	0.92
Range	1–82	3–50	
Duration of ribavirin therapy — mo			
Median	3	3	0.16
Range	1–18	1–6	

Table 2. (Continued.)

Variable	Patients with Sustained Virologic Response (N=46)	Patients without Sustained Virologic Response (N=13)	P Value
Duration of ribavirin therapy ≤3 mo — no. (%)	29 (63)	10 (77)	0.51
Initial ribavirin dose — mg/day			
Median	600	600	0.64
Range	29–1200	200–1000	
Dose reduction or interruption of ribavirin — no. (%)	11 (24)	6 (46)	0.17
Use of recombinant erythropoietin during ribavirin therapy — no. (%)	26 (57)	6 (46)	0.54
Blood transfusion — no./total no. (%)	5/45 (11)	2/13 (15)	0.65
Positive test for anti-HEV IgG antibodies at the initiation of ribavirin — no./total no. (%)	29/38 (76)	9/12 (75)	1.00
Positive test for anti-HEV IgM antibodies at the initiation of ribavirin — no./total no. (%)	43/44 (98)	12/13 (92)	0.41
HEV RNA concentration at the initiation of ribavirin — copies/ml			
Median	5,555,000	349,000	0.29
Range	3390–30,200,000	52,400–1,900,000	
Positive test for HEV RNA at mo 1 — no./total no. (%)	11/40 (28)	7/10 (70)	0.02

* Two variables with a univariate P value of less than 0.05 were included in a multivariate analysis. A higher lymphocyte count at the initiation of ribavirin was significantly associated with a sustained virologic response (odds ratio, 1.002; 95% confidence interval [CI], 1.001 to 1.004; P=0.008). A positive test for HEV RNA at month 1 was not significantly associated with a sustained virologic response (odds ratio, 0.20; 95% CI, 0.04 to 1.14; P=0.07).

found that the HEV-specific T-cell response can be recovered in transplant recipients with chronic infection after ribavirin therapy has induced HEV clearance.[19] However, in that report, it is unknown whether the HEV-specific T-cell response was recovered during ribavirin therapy, which would suggest a modulatory effect of ribavirin, or whether it occurred after HEV clearance.[39] It is unlikely that the use of ribavirin as monotherapy is responsible for HEV resistance because ribavirin has no known direct effect on a specific viral target. The recurrence of HEV replication after cessation of ribavirin therapy could be related to the lack of detection of HEV in the serum, though HEV replication may persist at other sites, such as the gut.

Owing to the retrospective nature of our study, this uncontrolled case series has several limitations: the number of patients studied was small; the actual level of immunosuppression that can play a role in HEV clearance was not assessed; care was clinically driven, so the doses and durations of ribavirin and the monitoring strategies differed among the patients and study sites; and ribavirin levels were not measured.

In conclusion, this retrospective, multicenter case series showed that ribavirin as monotherapy may be effective in treating chronic HEV infection. A 3-month course seems to be an appropriate duration for this therapy, though a longer therapy can be given to heavily immunosuppressed patients and those who still have viremia 1 month after the initiation of therapy. However, prospective studies are required to determine the most beneficial dose and duration of ribavirin therapy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. A. Louvet and P. Mathurin (Lille University Hospital), J. Gournay (Nantes University Hospital), C. Legendre (Paris Descartes University), and L. Alric, I. Cardeau-Desangles, O. Cointault, A. Del Bello, L. Esposito, J. Guitard, L. Lavayssière, J.M. Peron, M.B. Nogier, and D. Ribes (Toulouse University Hospital) for their help in the follow-up of the patients.

APPENDIX

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