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VIRAL HEPATITIS

Treatment of autochthonous acute hepatitis E with short-term ribavirin: a multicenter retrospective study

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Abstract

Background & Aims: Hepatitis E virus (HEV) genotypes 3 and 4 cause sporadic cases of infection in developed countries. Being elderly and having an underlying liver disease are the main risk factors for death in this population. Chronic infection has been described in immunocompromised patients. Ribavirin is now the antiviral treatment of choice in solid-organ-transplant recipients with chronic HEV infection. We hypothesized that early short-term treatment of acute HEV infection may be useful for patients with risk factors or undergoing chemotherapy. *Methods:* Between July 2010 and January 2014, 21 patients diagnosed with acute HEV infection were treated with ribavirin, at 600–800 mg/day for up to 3 months. All serum samples were positive for HEV RNA. *Results:* Nine patients were treated for severe hepatitis. Six patients were aged >70 years. Four patients were receiving an immunosuppressive therapy for an autoimmune disease and two patients were undergoing chemotherapy for a malignancy. Two patients received a fixed-dose regimen. For all other patients, ribavirin was stopped when HEV became undetectable in the serum. The median duration of ribavirin treatment was 26 days. Two patients developed severe anaemia. Two patients with encephalopathy died. One patient relapsed transiently. All patients were cleared of HEV and regained normalized liver-enzyme levels. Immunosuppressive treatment and chemotherapy could be resumed. *Conclusions:* Treatment of acute HEV infection using ribavirin seems safe and effective. Short-term treatment tailored to viraemia may be the best regimen for this indication.

Keywords
acute hepatitis – antiviral therapy – cirrhosis – hepatitis E – immunodeficiency

Abbreviations
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HEV, hepatitis E virus; PT, prothrombin time; γGT, γ-glutamyl transpeptidase.

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Key points

- Twenty-one patients with acute HEV infection were treated with short-term ribavirin. They were either at risk of developing acute liver failure, or were receiving an immunosuppressive therapy for an autoimmune disease or undergoing chemotherapy.
- The median duration of ribavirin treatment was 26 days.
- All patients had undetectable HEV RNA in a median time of 29 days.
- This study suggests short-term ribavirin is safe and effective in patients with acute hepatitis E.

Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis in the world (1, 2). HEV genotypes 1 and 2 are responsible for large outbreaks and sporadic cases in developing countries. HEV genotypes 3 and 4 are zoonotic infections and cause sporadic autochthonous cases of HEV infection in developed countries. It arises most frequently in older adults, particularly men, and therefore has been mistaken for drug-induced hepatitis (3, 4). A minority of patients with autochthonous HEV infection will develop acute or subacute liver failure. Such patients usually also have underlying chronic liver disease and/or are older, resulting in a higher mortality rate (5).

In recent years, cases of chronic HEV infection associated with progressive liver disease have been described in solid-organ-transplant recipients in developed countries (6, 7). In these patients, 3 months of ribavirin treatment can obtain a high sustained viral-response rate and is well tolerated (8). Prolonged cases of HEV infection have also been described in patients treated with chemotherapy (9). In these patients, effective treatment of the malignancy may be hindered by HEV viraemia or cytolysis.

Preliminary published case reports on isolated cases of acute hepatitis E treated with ribavirin have produced promising results (10–12).

We hypothesized that early short-term treatment of acute HEV infection may be useful for patients with risk factors of acute or subacute liver failure or who are undergoing chemotherapy. Here, we report the results from a French multicentre study on the treatment of patients with acute HEV infection.

Patients and methods

Study design

We conducted a French multicentre retrospective study between July 2010 and January 2013 (University Hospital Center of Toulouse, France; University Hospital Center of Nice, France; University Hospital Center of Marseille, France; Hospital Center of Pau, France; Hospital Center of Hyères, France).

Patients

Twenty-one patients diagnosed with acute HEV infection and who were treated with ribavirin were included in this study. All these patients had acute hepatitis characterized by elevated transaminase levels and their serum was positive for HEV RNA. Four of these patients lived in southeast France, and 17 in southwest France. The HBs antigen, anti-HBc antibodies and anti-hepatitis C virus antibodies, as well as serum hepatitis B virus DNA and hepatitis C RNA, were negative in all patients. In France 810 patients were diagnosed with HEV infection in 2012.

The patients' clinical characteristics and the indication for ribavirin treatment are summarized in Table 1. There were 14 men and 7 women, ranging in age from 30 to 85 years (median age 62 years). Patient 1 (12) and 8 (10) have already been described previously. Patients n° 1–4 and 9–21 came from southwest France and patients n° 5–8 from southeast France. Only one patient (patient n° 11) had travelled outside the country (Dominican Republic).

Nine patients were treated for severe or potentially severe hepatitis, defined by a low prothrombin time (PT) (≤60%). Among them, three had underlying alcoholic cirrhosis (patient n° 1, 5, and 21). Six patients were aged ≥70 years (70–85 years). Among the 21 patients, six had alcoholic cirrhosis. Some patients had multiple risk factors. Two patients were undergoing chemotherapy for a malignancy: one for breast cancer (docetaxel and FEC 100, patient n°10) and one for cholangiocarcinoma (gemcitabine and oxalipaltine, patient n°19). Chemotherapy for both these patients was halted when acute HEV infection was diagnosed. Four patients were treated because they were receiving an immunosuppressive therapy for an autoimmune disease: rheumatoid arthritis (methotrexate and steroids, patient n°3), juvenile arthritis (infliximab and methotrexate, patient n°11), psoriatic arthritis (methotrexate, patient n°12) and ankylosing arthritis (infliximab, patient n°15). One patient >70 years old with chronic myeloid leukaemia (patient n°9) had thrombocytopenia. Another patient with chronic lymphocytic leukaemia in remission (patient n°14) received ribavirin treatment because of poor tolerance and severe hyperthermia (40°C over several days). None of them was receiving a specific treatment for their haematological malignancy. This study was approved by Toulouse University Hospital IRB. Patients were given ribavirin after having given their informed consent.

Treatment

Ribavirin (Copegus; Roche, Boulogne-Billancourt, France) was initially given at 600–800 mg/day in two separate doses. Ribavirin doses were chosen according to the weight of the patient; creatinine values were then adapted to haemoglobin levels. In two patients (patients n°4 and n°9), ribavirin treatment was arbitrarily scheduled for 3 months, as has been previously prescribed for

Table 1. Patients' characteristics at baseline

	Patients n°	Age (years)	Gender	Comorbidities
Cirrhosis (PT >60%)	2	75	M	Old age
	18	50	M	
	20	69	M	
Immunosuppressive therapy	11	30	F	Juvenile arthritis
	12	62	M	Psoriatic arthritis
	15	50	F	Ankylosing arthritis
	3	70	M	Old age and Rheumatoid arthritis
Chemotherapy	10	54	F	Breast cancer
	19	71	F	Cholangiocarcinoma and old age
PT ≤60%	1	47	M	Cirrhosis
	5	46	M	Cirrhosis
	21	50	M	Cirrhosis
	6	62	M	
	7	44	M	
	8	61	M	
	13	64	M	
	17	63	F	
	4	70	M	Idiopathic Thrombocytopenic Purpura and old age
Others (haematological malignancy or old age)	9	77	F	Chronic myeloid leukaemia and Old age
	14	50	F	Chronic lymphocytic leukaemia
	16	85	M	Old age

F, female; M, male; PT, Prothrombin time.
Old age was defined as age above 70 years old.

allograft recipients with chronic hepatitis E (1). For all other patients, duration of treatment was tailored for viral clearance: e.g. it was stopped when HEV RNA was undetectable in the serum.

Subjects were followed up at the physician's discretion. Sixteen patients had a viral load dosage at baseline (i.e. patients from southwest France) and were followed every week until viral clearance. At each visit, liver (aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γGT), serum creatinine, as well as haemoglobin levels, white blood-cell counts and lymphocyte and platelet counts were performed. HEV viraemia was also determined at each visit.

Methods

Anti-HEV antibodies were detected using Wantai kits (Wantai Biologic Pharmacy Enterprise, Beijing, People's Republic of China) and the EIAgen HEV IgM kit, Adaltis (Ingen, Chilly-Mazarin, France). The HEV RNA from serum was quantified using a homebrew real-time PCR that targeted the ORF3 region (13). The limit of detection was 100 copies/mL. The detected strains were typed by sequencing an ORF2 fragment, as reported previously (14). We tried but failed to sequence the strains from six patients.

Statistical analyses

Data are represented as medians (ranges). Quantitative variables were compared using the Friedman and Wilcoxon tests. A P-value <0.05 was considered statistically significant.

Results

Clinical presentation of hepatitis E

The acute hepatitis episode was symptomatic in all patients. Thirteen patients presented with jaundice. Nineteen patients had asthenia, six had a fever, five had myalgia and two had abdominal pain. None had neurological symptoms except two patients (n°5 and 21) with underlying alcoholic cirrhosis that presented encephalopathy. All patients required a hospitalization. Median hospital stay was 6.5 days (range: 0–116).

Biochemical parameters at baseline

Liver and virological parameters at baseline are summarized in Table 2. Major elevation of transaminases was observed in all cases, with median levels of AST and ALT of 883 IU/L (range: 72–7477) and 1415 IU/L (range: 128–7771) respectively. The median level of γ-GT was 500 IU/L (range: 87–1383).The median total bilirubin level was 80.5 μmol/L (range: 8–550). Median PT was 70% (range: 18–100). Eight patients had a PT of <50%.

All patients had serum HEV RNA positive but concentrations were available only for 16 patients. Before ribavirin therapy, median HEV viraemia was 233 500 copies/mL (1270–190 000 000). In addition, HEV RNA

Table 2. Liver biochemical tests and viroglogical parameters at baseline

	Liver parameters					Virological parameters		
Patient n°	AST (IU/L)	ALT (IU/L)	γ-GT (IU/L)	Bilirubin (μmol/L)	PT (%)	HEV RNA levels Copies/mL	Genotype Log	
1	2593	2724	1383	84	49	11 800	4.1	ND
2	784	1656	284	42.7	70	10 700	4.0	ND
3	1182	2157	182	13.2	91	1270	3.1	3c
4	2938	2374	606	72	18	5 720 000	6.8	3f
5	1829	1415	344	387	27	ND	ND	ND
6	1588	2124	1294	74.5	48	ND	ND	4
7	6218	7771	327	218	21	ND	ND	3f
8		4565		550	38	ND	ND	3f
9	90	140	152	14	100	368 000	5.6	3f
10	883	1099	243	8	81	23 600	4.4	3f
11	826	1118	357	20.5	100	471 000	5.7	3f
12	584	1190	738	28	99	1 330 000	6.1	3c
13	7477	6219	372	33	34	190 000 000	8.3	3f
14	201	308	319	25	71	2 090 000	6.3	3f
15	72	142	87	8	91	1610	3.2	ND
16	719	833	125	269	63	14 700	4.2	3f
17	3339	4266	134	366	60	5 510 000	6.7	3f
18	168	128	904	173	75	6650	3.8	ND
19	2078	1299	1180	89	90	322 000	5.5	3c
20	1513	1482	565	59	81	125 000	5.1	3f
21	153	136	411	502	41	ND	ND	ND
Median (range)	883 (72–7477)	1415 (128–7771)	500 (87–1383)	80.5 (8–550)	70% (18–100).	233 500 (1270–190 000 000)		

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma glutamyl transpeptidase; ND: not determined; PT, prothrombin time.

was tested in stools for 12 patients: 10 were positive (patients n° 2, 4, 5, 9, 13, 14, 16, 17, 19, 20), while patients n°1 and 18 were negative. Interestingly, patient n°9 had positive HEV RNA but had negative IgM and IgG tests. Patient n°16 had negative IgM but positive IgG and two others patients (n°13 and 15) had positive IgM and negative IgG. The detected strains were sequenced in 15 patients. One patient from southeast France was genotype 4, and all other patients were genotype 3.

Ribavirin therapy

Ribavirin therapy is summarized in Table 3. Ribavirin was started at daily doses of 1200 mg in 2 patients, 1000 mg in 12 patients, 800 mg in 3 patients and 600 mg in 4 patients. Initial mean daily dose was 900 mg (±192); thereafter, ribavirin doses were adapted according to haemoglobin levels. During this study, ribavirin doses were reduced for two patients because of severe anaemia (patients n° 9 and 13). In addition, patient n°9 was treated with EPO (epoietin beta 30 000 units/week) and was given a blood transfusion of two units. Two patients received a fixed 3-month regimen (patients n° 4 and 9). For all other patients, ribavirin was stopped when HEV became undetectable in the serum. The median duration of ribavirin treatment was 26 days (range: 3–90).

Virological response

Median time after ribavirin initiation to obtain undetectable RNA was 29 days (Table 3). The HEV RNA was cleared in all patients alive at 6 weeks. One relapse was observed. It occurred in patient n° 16. His initial viral load was 4.2 log-copies/mL (14 700 copies/mL) (Table 2). He was treated for 20 days with ribavirin, which was stopped when viraemia became undetectable in the serum. A further test a week later showed a viral load of 2.1 log-copies/mL (134 copies/mL), with no increase in liver tests. Ribavirin was not reintroduced. All subsequent controls were negative (at 16 days later, at a month later, and by 8 months later). No other relapses occurred in any of the other patients. All patients alive were cleared of HEV and regained normalized liver enzymes levels.

Outcomes of patients

Two patients died of terminal liver failure (patient n°5 and 21). Both had encephalopathy and ascites at onset, as well as underlying alcoholic cirrhosis. They were the only patients with encephalopathy or ascites. The four other patients with underlying liver disease survived.

All the other patients survived with no relapses. All patients aged ≥70 years survived.

Table 3. Ribavirin therapy

Patient n°	Dose (mg/day)	Duration (days)	Ribavirin dose reduction	Virological response	Time for undetectable RNA (days)
1	1000	10	No	SVR	13
2	1000	5	No	SVR	23
3	1000	7	No	SVR	25
4	600	90	No	SVR	48
5	600	15	No	Death	NA
6	800	11	No	SVR	30
7	800	3	No	SVR	35
8	800	21	No	SVR	30
9	600	90	Yes	SVR	78
10	1000	52	No	SVR	18
11	1000	33	No	SVR	16
12	1000	35	No	SVR	50
13	1200	51	Yes	SVR	50
14	1000	31	No	SVR	43
15	1000	4	No	SVR	19
16	1000	20	No	SVR	36
17	1000	35	No	SVR	28
18	1200	7	No	SVR	27
19	1000	26	No	SVR	23
20	1000	31	No	SVR	35
21	600	28	No	Death	NA

NA, not available (patients died before the second PCR or did not have a second PCR); SVR, sustained virological response.

Two patients were undergoing chemotherapy when they developed acute HEV (patients n°10 and 19): this was halted at the time of diagnoses. Patient n°10 was then able to resume chemotherapy after a delay of 4 weeks and patient n°19 after a delay of 9 weeks.

Four patients were treated because they needed to pursue their immunosuppressive treatment in the context of an inflammatory rheumatic disease. Patient n°3 was treated with methotrexate (15 mg/week) for rheumatoid arthritis. Methotrexate was resumed after 2 months. Patient n°11 was treated with steroids (6 mg/day), methotrexate (20 mg/week) and had just had her third perfusion of anti-TNF-α. Both methotrexate and anti-TNF-α perfusions were halted and resumed 14 weeks later. Patient n°12 was treated with methotrexate (20 mg/week) for psoriatic arthritis. Methotrexate was resumed after 12 weeks. Patient n°15 was treated for ankylosing arthritis with methotrexate (10 mg/week) and anti-TNF-α perfusions for 7 weeks. The anti-TNF-α perfusions were resumed after 7 weeks, and methotrexate was halted.

Discussion

This work describes ribavirin treatment of patients presenting an acute HEV infection. In developed countries, both HEV genotypes 3 and 4 are detected, but HEV-3 is the most frequent. Being elderly and having an underlying liver disease are the main risk factors for encephalopathy and death (1, 5, 15).

In solid-organ-transplant recipients, chronic infections have been reported to have a 10% risk of progression to cirrhosis (6, 8). Ribavirin monotherapy used as a fixed 3-month regimen is now the first treatment option for solid-organ-transplant recipients with chronic HEV (1, 8). In patients who receive immunosuppression because of chemotherapy, viraemia can be prolonged (9) and patient-to-patient transmission has been described in this setting (16). The rationale of this study was therefore that it may be valuable to suppress viral replication in these high-risk populations: i.e. patients at a higher risk of dying (older patients with underlying cirrhosis, and low prothrombin time) and patients that need to continue treatment that is contraindicated because of viraemia or severe cytolysis (i.e. receiving chemotherapy or immunosuppressive agents for an autoimmune disease). The indication for treatment was severe or potentially severe hepatitis in 9 patients, age ≥70 years in six patients, immunosuppressive therapy for an autoimmune disease in four patients and chemotherapy for a malignancy in two patients. Ribavirin was tailored to viral clearance in all but two patients. This work shows that tolerance of ribavirin was excellent in the context of acute HEV infection and when liver tests were severely elevated. Fifteen patients had transaminases levels of >1000 IU/L and seven patients had bilirubin levels of >100 μmol/L. The only adverse event reported was anaemia. The good tolerance was probably in part because of the short duration of the treatment.

Ribavirin therapy of acute HEV3 or HEV4 infection induced rapid viral clearance. Interestingly, only one patient had a relapse shortly after ribavirin was stopped, but this patient's viral load was 2.1 log-copies/mL, which is very close to the limit of detection for this PCR

technique (2.0 log-copies/mL). This relapse had no consequences on the evolution of liver-enzyme levels or clinical outcome. It could be argued that one should control negative viraemia with a second blood test before halting ribavirin treatment. However, no other patient suffered a relapse: this indicates that, overall, for the treatment of acute HEV, a short duration treatment tailored to viraemia is probably adequate.

Two patients died despite treatment: both had decompensated liver disease with ascites and encephalopathy when ribavirin was initiated. This indicates that ribavirin therapy was started too late, and is a clear incentive to diagnose acute HEV as rapidly as possible in this population. Further prospective studies are needed to determine the natural history of HEV in this population of patients with cirrhosis. If ribavirin is to play a role, it is likely that therapy needs to be started as soon as possible.

Six patients received ribavirin because they had developed acute HEV infection while also receiving either chemotherapy for cancer or an immunosuppressive agent for inflammatory rheumatism. Ribavirin was very well tolerated and there was no relapse of HEV, even when chemotherapy or the immunosuppressive agents were reintroduced.

Case reports describing patients with acute HEV-3 infection treated with ribavirin have been recently published (10–12). The first treatments of acute hepatitis were for patients with acute HEV-3 and underlying cirrhosis (12). In these preliminary case reports, ribavirin was well tolerated and patients recovered without any relapses. A successful 3-week treatment with ribavirin, for a patient with severe acute HEV-3 but no underlying liver disease, has been also reported (10).

Treatment of four patients with acute HEV1 has recently been reported in a study from New Delhi (11). Ribavirin was used for a median duration of 12 weeks (range: 3–24). HEV RNA was undetectable in 3–8 weeks and there were no serious side effects.

This study is not randomized: therefore, we cannot conclude that antiviral treatment effectively shortened the viraemia period or that it was efficient in terms of disease outcomes. Also, a randomized study is, unfortunately, probably impossible to fulfil because of the small number of patients in developed countries that develop autochthonous HEV and have risk factors for an unfavourable outcome.

Conclusion

We conclude that the treatment of acute HEV infection using ribavirin is safe and that short-term treatment tailored to viraemia is the best regimen for this indication. Ribavirin could be an effective therapeutic option for patients with acute HEV infection in specific situations: (1) older patients, (2) patients with underlying liver disease, (3) patients undergoing chemotherapy or (4) those receiving immunosuppressive treatments for an autoimmune disease.

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