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CLINICAL STUDIES

Ribavirin treatment of acute and chronic hepatitis E: a single-centre experience

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Abstract

Background: The role of ribavirin for treatment of severe acute or chronic hepatitis E virus (HEV) infection is not well defined. *Aims:* To investigate the applicability and efficacy of ribavirin therapy in acute and chronic HEV infections within a large single-centre cohort. *Materials & Methods:* Clinical courses of forty-four German HEV-infected individuals were analysed. *Results:* In a prospective case series, we observed spontaneous recovery from acute symptomatic HEV-infection in 10/11 immunocompetent individuals. Ribavirin therapy was initiated in one patient with severe acute HEV-genotype-1e infection who rapidly improved liver function and cleared HEV. Of 15 organ transplant recipients with prolonged HEV viraemia, reduction in immunosuppression led to HEV-clearance in three patients, while ribavirin therapy was initiated in 11 subjects. A rapid response with undetectable HEV-RNA occurred in nine subjects. One patient died after experiencing a virological breakthrough associated with ribavirin dose reduction because of severe anaemia. *Discussion:* Ribavirin is a safe treatment option for HEV infections. However, the optimal dose of ribavirin for the treatment of chronic hepatitis E remains to be determined as treatment failure may occur.

Hepatitis E is caused by infection with the hepatitis E virus (HEV) (1–3). While hepatitis E was mainly considered as a travel-associated liver disease, an increasing number of autochthonous zoonotic HEV infections has been reported in Western countries in recent years (2). Acute hepatitis E takes a clinically silent and asymptomatic, self-limited course in almost all immunocompetent patients (1, 4). Few individuals develop severe acute hepatitis E, which may progress to liver failure in single patients (1). Some preliminary evidence suggests that acute hepatitis E may take more often a severe course in HEV genotype 1 than in HEV genotype 3 infection (5). There is no established treatment concept for acute hepatitis E. Liver transplantation may be the only therapeutic option for individuals with HEV-induced liver failure. Ribavirin has recently been applied to three patients with severe autochthonous acute hepatitis E leading to rapid recovery (6, 7). Ribavirin has also been shown to be effective in four patients with acute HEV genotype 1 infection (8). However, it is still unclear which patients with acute hepatitis E may benefit from antiviral therapy.

Chronic courses of hepatitis E have been described in different cohorts of immunocompromised individuals (1). Chronic hepatitis E can lead to progressive liver disease with biochemical and histological evidence of inflammation and fibrosis. Several cases of rapid

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development of liver cirrhosis within few years of infection were reported in organ transplant recipients with persistent HEV infection (1). Thus, treatment concepts are urgently needed for chronic hepatitis E to prevent HEV-associated morbidity and mortality. Three different therapeutic approaches have been evaluated in patients with chronic hepatitis E. Firstly, immunosuppressive medication might be reduced which could enhance antiviral immunity leading to control of HEV replication. We recently demonstrated an association between HEV-specific T-cell responses and recovery from chronic hepatitis E (9). However, this strategy has been successful only in a minority of patients (10) and is not applicable to transplanted patients with a high risk of rejection. Secondly, few patients with persistent HEV infection have been treated successfully with pegylated interferon alpha (11, 12). Type I interferons cannot be used in many organ transplant recipients as rejections could be triggered by interferon alpha. Moreover, prolonged therapies with interferon alpha may be required being associated with significant side effects and costs. Finally, ribavirin monotherapy of chronic hepatitis E has been successfully applied in two small case series leading to sustained HEV RNA clearance and ALT normalization in 6 of 8 patients (13, 14). Still, the optimal dose and duration of ribavirin therapy of chronic hepatitis E need to be defined.

The aim of this study was to investigate the applicability and efficacy of ribavirin therapy in acute and chronic HEV infections within a large single-centre cohort.

Patients and methods

Study cohort

Forty-four German HEV-infected individuals including 11 immunocompetent patients with acute symptomatic hepatitis E and 33 solid organ transplant recipients with post-transplant HEV-infection were included in this study between February 2008 and May 2012. Prolonged HEV viraemia developed in 15 organ transplant recipients (46%). Prolonged hepatitis E has been defined as proven HEV viraemia in immunosuppressed individuals with elevated ALT levels for more than 2 months. This study has been approved by the local ethical committee of Hannover Medical School. Individual courses of two liver transplant and four heart transplant recipients have been reported previously in part (15, 16).

All patients were tested for HEV RNA and anti HEV IgG. Additionally, stored sera of patients were tested, if available, to determine the time point of exposure to HEV.

All patients were recruited at Hannover Medical School between March 2008 and May 2012.

AntiHEV and HEV RNA testing

Anti HEV immunoglobulin G antibodies were tested with the MP Diagnostic assay (MP Biomedicals, formerly Genelabs Diagnostics, Singapore) according to the manufacturer's instructions as reported previously (15, 16). HEV RNA testing was performed by nested PCR also as described previously (15, 16). To determine HEV viral load, a quantitative real-time PCR was performed using the Cobas Taqman platform similar to our previous studies in hepatitis D virus infection (17).

Treatment of hepatitis E

Ribavirin (Rebetol, MSD, Munich, Germany or Copegus, Roche, Grenzach-Wyhlen, Germany) was applied twice daily orally with an initial daily dose of 600–1000 mg, depending on the patients' haemoglobin level and comorbidities. Dose reductions were performed if haemoglobin levels declined and/or patients developed symptoms associated with anaemia. The planned treatment duration of chronic hepatitis E was 5 months, as previous reports indicated that a shorter treatment duration of 3 months may be associated with viral relapse (14).

Statistics

Data for the different patient groups are presented in medians and ranges. A comparison of categorical data between groups was performed using the chi-square test. Comparison of quantitative data between groups was performed using the Mann–Whitney test. A P-value < 0.05 was considered significant.

Results

Immunocompetent individuals

Acute hepatitis E was diagnosed in 11 subjects (9 male/2 female, median age 57 years, range 36–76 years). The median peak ALT level was 1859 IU/l (range 263–5196 IU/l), 82% of the patients were icteric (9/11) with a bilirubin level of more than three times upper the limit of normal (median 145 μmol/l, range 11–652 μmol/l). The median of INR was 1.2 (range 1.0–1.8). All HEV infections but one were autochthonous and all of these patients showed a spontaneous recovery from acute hepatitis E without any antiviral treatment intervention. The only travel-associated case of acute hepatitis E was a HEV genotype 1e infection of a 42-year-old women who acquired HEV in Eritrea. The clinical course of this patient is shown in Fig. 1. Treatment with ribavirin was initiated once liver function worsened as determined by prothrombin values and we became aware that this patient was infected with HEV genotype 1e, which possibly could be associated with a higher risk for severe courses than autochthonous genotype 3 infections. ALT and AST values rapidly declined within the first three days after initiation of treatment and INR values normalized. Treatment with ribavirin was continued

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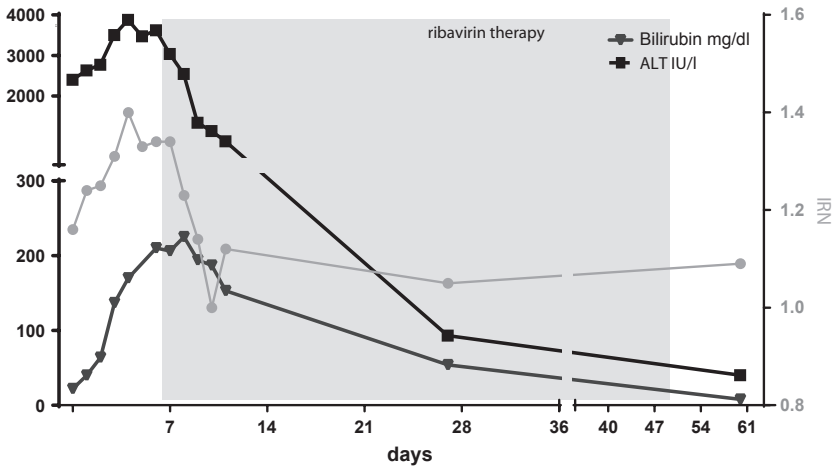

Fig. 1. Course of bilirubin, ALT and INR in a patient with acute hepatitis E, treated with ribavirin for 6 weeks.

Table 1. Characteristics of solid organ transplant recipients with HEV infection

	Age	TX-organ	Sex	Immunosuppression	Peak ALT	Peak INR	Therapy	Clearance of HEV within less than	Outcome
OLT 1	34	Liver	m	tac, mmf, decortin	239	1.3	Reduction of IS	3 months	SVR (follow-up >2 years)
OLT 2	40	Liver	m	ciclo, mmf, decortin	555	1.0	Reduction of IS	30 months	SVR (follow-up >2 years)
KTR 1	43	Kidney	m	tac, mmf, decortin	359	1.0	Reduction of IS	6 months	SVR (follow-up >2 years)
KTR 2	65	Kidney	m	ciclo, mmf, decortin	1566	1.0	Ribavirin	1 month	SVR (follow-up >2 years)
KTR 3	50	Kidney	m	ciclo, mmf, decortin	160	1.0	Ribavirin	2 months	SVR (follow-up >5 months)
KTR 4	40	Kidney	m	tac, mmf	342	1.1	Ribavirin	2 months	SVR (follow-up >4 months)
KTR 5	54	Kidney	m	ciclo, sirolimus	2053	1.1	Ribavirin	1 month	SVR (follow-up >4 months)
HTR 1	50	Heart	f	ciclo, decortin, everolimus	217	1.0	Ribavirin	2 month	SVR (follow-up >2 years)
HTR 2	66	Heart	m	ciclo, decortin, everolimus	209	1.1	Ribavirin	1 month	SVR (follow-up >2 years)
HTR 3	57	Heart	m	ciclo, decortin, azathioprine	211	1.1	Ribavirin	1 month	SVR (follow-up >2 years)
HTR 4	58	Heart	m	tac, decortin, everolimus	315	1.1	Ribavirin	No clearance	Patient died from liver cirrhosis-associated complications
LuTR 1	48	Lung	f	tac, mmf, decortin	89	1.4	Ribavirin	2 months	SVR (follow-up >2 months)
LuTR 2	56	Lung	f	ciclo, mmf, decortin	254	1.1	Ribavirin	2 months	SVR (follow-up >7 months)
LuTR 3	32	Lung	m	ciclo, mmf, decortin	270	1.0	Ribavirin	No clearance	Patient died because of failure of lung transplant (6 weeks after begin of treatment)
LuTR 4	41	Lung	m	tac, mmf, decortin	215	1.6	No therapy	No clearance	Patient died before diagnosis of HEV infection (retrospectively identified)

for 6 weeks (Fig. 1). No virological or biochemical relapse was observed after therapy.

Immunocompromised patients

Prolonged HEV viraemia developed in 15 of 33 organ transplant recipients (Table 1). One lung transplanted patient who was identified as part of a retrospective screening protocol died because of decompensated liver cirrhosis before the diagnosis of HEV infection was established. HEV RNA became negative after reduction in immunosuppressive therapy in three individuals. Ribavirin therapy was initiated in 11 subjects. ALT levels rapidly improved in all patients after ribavirin was started (Fig. 2). HEV RNA tested negative in the blood in nine patients after a treatment duration of 3–6 weeks (median 5 weeks). No biochemical or virological relapse occurred when treatment was stopped (n = 9). The follow-up period in patients successfully treated with ribavirin ranged from 2 months to more than 2 years (median 7 months). One patient could be treated for only 6 weeks as he experienced a fatal lung graft failure

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(LuTR 3). A heart transplant recipient (HTR 4) who was viraemic for 4 years and who had already developed liver cirrhosis did not become HEV RNA negative during treatment. HEV RNA levels initially declined by approximately 3 log copies/ml and increased again to baseline levels after ribavirin dose reduction was necessary as a result of severe anaemia. The dose of ribavirin was transiently increased again after administration of blood transfusions, but HEV RNA levels remained at baseline levels. ALT levels transiently normalized and slightly increased during the virological rebound, but remained at lower than baseline values with continued low dose ribavirin (200 mg/d) (Fig. 2). However, the clinical condition worsened constantly and the patient died from hepatic decompensation 9 months after treatment failure. The individual course of this patient has partially been described in a previous publication (16).

Safety of ribavirin treatment

Ribavirin therapy was associated with a decline in haemoglobin levels of at least 2 g/dl in nine patients. The mean haemoglobin decline was 3.4 g/dl (3.4 range 0–7.9 g/dl). Four subjects developed grade II anaemia (haemoglobin levels below 9.5 g/dl) and one further subject grade III anaemia (haemoglobin levels below 8 g/dl) during therapy. The latter patient was a kidney transplant recipient (KTR 5) without any history of cardiac disorders who developed atrial fibrillation during the episode of severe anaemia. Ribavirin dose reduction was required in five patients (45%; two heart transplant recipients, two kidney transplant recipients, one lung transplant recipient). Dose reduction was performed in 200 mg steps.

Discussion

This is so far the largest study on ribavirin-treatment of HEV-infected patients. Ribavirin seems to be an effective option against HEV and successful therapy may prevent liver related mortality. Ribavirin mono-therapy induced clearance of prolonged HEV infection in immunocompromised individuals and thus confirmed two earlier reports from France (13, 14). All patients who cleared HEV normalized liver enzymes, while one untreated individual and a patient with treatment failure died from liver disease. A main difference of our therapeutic approach to the previous studies was that the treatment was applied for 5 months instead of 3 months. We chose this longer treatment duration based on the assumption that longer treatment would reduce the risk of HEV relapse after stopping of ribavirin therapy. It is well known that prolonged viral suppression is associated with lower relapse rates in hepatitis C (18). Indeed, and in contrast to the French experience, we did not observe any virological relapse after the end of 5 months of ribavirin therapy of hepatitis E. This observation would be consistent with many studies in hepatitis C showing that a minimum duration of viral suppression is required to achieve viral eradication (18). Nevertheless, the optimal treatment duration for individual patients with hepatitis E (e.g. 2, 3, 4, 5 or 6 months) needs to be defined in future studies. In particular, the question is not answered yet whether response-guided therapy based on the initial viral decline may also be applicable in HEV infection similar to hepatitis C (18).

Another yet unresolved question in ribavirin therapy of hepatitis E is the optimal dose of ribavirin. For hepatitis C a dose-dependent effect of ribavirin to induce HCV clearance has been demonstrated in numerous studies. While a daily dose of 600 mg seems to be sufficient in most hepatitis E cases, we here describe a patient where ribavirin dose reduction to 200 mg daily was associated with viral rebound and clinical evidence of resistance. This observation has important clinical implications as we would suggest avoiding dose

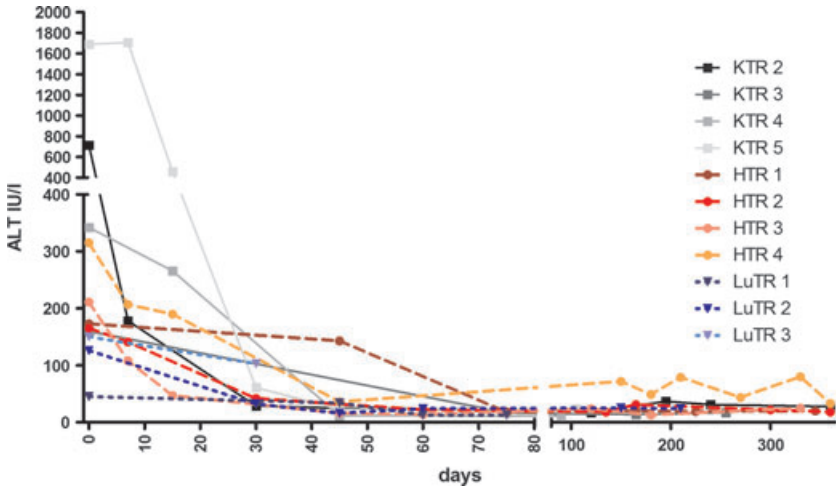

Fig. 2. One-year follow-up (from the beginning of ribavirin treatment) of ALT levels in transplant recipients treated with ribavirin. Patient HTR 4 suffered from viral breakthrough. Patient LuTR 3 died from non liver or therapy-associated death.

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reductions as much as possible. Future studies need to investigate the underlying pathomechanisms that are causative for ribavirin resistance. We are currently investigating if distinct amino acid changes may confer virological resistance to ribavirin. In addition, ribavirin may have other indirect mode of actions leading to suppression of viral replication, which still need to be determined for HEV (1).

In addition to successful treatment of autochthonous chronic hepatitis E, we here demonstrate, for the first time, that ribavirin seems to be effective not only in HEV genotype 3 infection but also in acute HEV genotype 1 infection. Thus, even though the detailed mode of action of ribavirin against HEV is still unknown, ribavirin seems to have a broad antiviral activity across HEV genotypes. Moreover, we provide a rationale to further explore the efficacy of ribavirin in patients with acute hepatitis E to prevent progression to liver failure or to shorten the acute symptomatic phase of hepatitis. However, we also show that autochthonous acute hepatitis E seems not to require any antiviral intervention in the far majority of immunocompetent patients in Western countries.

Treatment with ribavirin is easy and generally well tolerated and safe. Still, ribavirin can cause side effects including anaemia, which may be of particular importance in individuals with multiple comorbidities. Alternative treatment options for hepatitis E should therefore be developed and evaluated. In our hands, reduction in immunosuppression may safely be applied at least in liver transplant recipients, but is of limited value in heart transplant recipients and lung transplant recipients. Moreover, the role of distinct immunosuppressive agents in hepatitis E requires further investigation. While the use of tacrolimus has been associated with a higher likelihood to develop chronic hepatitis E (10), we recently obtained some evidence that mycophenolate may be associated with spontaneous clearance of HEV (16).

In conclusion, ribavirin is a safe treatment option for both immunocompetent individuals with severe acute hepatitis and solid organ transplant recipients with HEV infection. However, as treatment failure may occur, the optimal dose of ribavirin for the treatment of hepatitis E remains to be determined.

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