Rimantadine for Treatment of Hepatitis C Infection in Liver Transplant Recipients

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Hepatitis C recurrence after liver transplantation is a serious problem, leading to increased graft loss and morbidity in some individuals. Treatment with interferon and other agents is controversial and not highly efficacious. The use of an effective antiviral agent to reduce or eliminate viral burden is desirable. To this end, we performed an open-label pilot trial to determine if rimantadine would show antiviral activity against hepatitis C virus (HCV) in the posttransplantation setting. Eleven patients with recurrent post–liver transplantation disease, characterized by transaminase level abnormality and HCV RNA in serum and liver biopsy specimens consistent with HCV infection were offered enrollment onto the study. Patients were treated for 12 weeks with rimantadine, 100 mg orally twice daily, and followed up after treatment for up to 8 additional weeks. Serum was collected at 2-week intervals to assess transaminase and HCV RNA levels. Nine patients completed the planned course of therapy. There was no significant change in serum alanine aminotransferase levels during treatment. No patients cleared HCV RNA from the serum, and fluctuations in the viral titer were not clearly associated with the initiation and completion of the active-treatment phase. Rimantadine was well tolerated, with only one patient who stopped therapy for perceived side effects. We conclude that rimantadine monotherapy has no role in the management of recurrent hepatitis C after liver transplantation.
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Hepatitis C virus (HCV) infection has emerged as the leading indication for liver transplantation in the United States. After liver transplantation, there is almost universal recurrence of HCV in the graft. Wright et al[1] showed that 95% of the patients with pretransplantation infection developed hepatitis C viremia posttransplantation. In terms of clinical outcomes, Gane et al[2] reported that at 6 months posttransplantation, 88% of the patients had evidence of chronic hepatitis on liver biopsy. Follow-up for up to 51 months showed that 8% had progressed to cirrhosis, whereas the majority of patients with shorter follow-up had mild to moderate liver injury. Graft loss was more common in HCV-reinfected patients than in other index-disease groups.[2,3] Some patients develop a severe, progressive cholestatic form of liver disease that is not generally observed in immunocompetent patient cohorts.[4]

The treatment of hepatitis C in the posttransplantation patient has been controversial, and only limited data are available. Interferon therapy, which represents the mainstay of treatment in the immunocompetent host, has been used with varying responses.[5,6] Feray et al[6] raised concerns about the increased risk for rejection events with this therapy. Ribavirin was also studied as a single-agent therapy for posttransplantation HCV infection, and no improvement in viral titer or histology was noted.[7]

Rimantadine hydrochloride is a synthetic antiviral agent structurally and pharmacologically related to amantadine hydrochloride. The agent is approved by the Food and Drug Administration for the treatment and prophylaxis of influenza A and is believed to be four- to tenfold more active than amantadine. In immunocompetent individuals, one report suggests that amantadine may have antiviral efficacy against hepatitis C, as evidenced by improved viral clearance among patients previously classified as interferon treatment failures.[8] Because rimantadine is related to, but more active than, amantadine, we selected this agent as a candidate drug for the treatment of chronic hepatitis C in the liver transplant population. An open-label, short-term pilot trial was performed to determine if rimantadine has efficacy against HCV as single-

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agent therapy in terms of virological and biochemical response outcomes.

Methods

Patients

Study candidates included adult patients (>18 years of age) who had undergone orthotopic liver transplantation at the University of Cincinnati Medical Center (Cincinnati, OH) 3 or more months before enrollment. All patients had evidence of recurrent HCV infection posttransplantation, evidenced by alanine aminotransferase (ALT) level abnormality (>35 U/L), HCV enzyme-linked immunosorbent assay reactivity, HCV RNA–positive serum, and a liver biopsy specimen consistent with chronic HCV reinfection within 3 months of randomization. Exclusion criteria included serious, life-threatening illness that would likely preclude full treatment and follow-up, pregnancy, and the inability to provide informed consent. Cirrhosis did not constitute a specific exclusion category.

Treatment and Laboratory Evaluation

Patients meeting the admission criteria were offered study entry and signed informed consent documents that were previously approved by the institutional review board. Patients were treated in an open-label fashion with rimantadine, 100 mg orally twice daily. Total treatment time was 12 weeks. A dose reduction to 100 mg was permitted if the patient experienced drug-related side effects. The posttreatment follow-up was 8 weeks.

Baseline laboratory data were obtained within 1 week of drug initiation and included a hepatic profile, complete blood count, HCV RNA by the branched-chain method, and a serum β-human chorionic gonadotropin level in women of childbearing potential. Specimens were also collected at 2-week intervals throughout the treatment phase, including a hepatic profile, complete blood count, and quantitative HCV RNA. Samples were collected at 2- to 4-week intervals during the posttreatment follow-up phase.

HCV RNA was tested by the Quantiplex 2.0 method (Chiron Corp, Emeryville, CA) in accordance with the manufacturer's instructions. This assay has a sensitivity of 0.2×10^6 HCV Eq/mL. Serum samples for this assay were separated from the clot within 3 hours of collection and stored in aliquots at −70°C until batch testing was performed. Genotype characterization was performed by a serological method, as previously described and validated, using Chiron strip immunoblast assay (SIA) kits.[9]

Results

Eleven patients met the entry criteria and provided signed informed consent. There were 9 men and 2 women. One man decided not to participate before taking any study medication. Therefore, 10 patients were treated with rimantadine. Among these 10 patients, the majority had stable liver disease with mild serum transaminase level abnormalities, but 1 patient had rapidly progressive HCV reinfection with bridging fibrosis less than 1 year posttransplantation. The racial distribution included 80% white and 20% black patients. The mean age was 46.3 years and ranged from 40 to 56 years.

The mean baseline ALT level was 129 ± 32.9 (standard error of the mean) U/L and ranged from 38 to 381 U/L. For the 10 patients who underwent treatment, the mean HCV RNA titer before drug initiation was 30.6 ± 11.24 mEq/mL and ranged from 0.46 to 120 mEq/mL. Five patients had virus classified as genotype 1 by the SIA technique; 1 patient was type 1 or 3, 1 patient was type 3, and 3 patients were untypeable.

Of the 10 patients who started therapy, 9 patients completed the planned 12-week course, and 1 patient dropped out because of perceived side effects. Mean and individual serial ALT levels during treatment are shown in Figure 1. ANOVA failed to show any meaningful difference between treatment time points. Only 1 patient normalized ALT level, but this was attributed to random variation because his pretreatment ALT level was only slightly greater than the upper limit of normal.

HCV RNA levels for each patient are shown in Figure 2. The mean RNA values at each interval were analyzed by ANOVA, which failed to show statistically meaningful differences. In patients in whom serum HCV RNA levels appeared to decrease during treatment, no levels decreased to less than the level of detection for the assay (200 000 HCV RNA Eq/mL). Furthermore, in patients in whom the viral titer decreased, the titer did not increase during the posttreatment follow-up phase, suggesting that this variability was attributable to other factors.

In general, the drug regimen was well tolerated. Clinically, only 2 patients complained of severe fatigue, flu-like symptoms, and nausea while receiving rimantadine. One such patient discontinued treatment within 2 weeks of initiation. Two patients had severe adverse events characterized by hospitalization, including 1 patient with pancreatitis and 1 patient with transient but severe nausea, vomiting, and dehydration. None of these events were attributed to the study drug because they

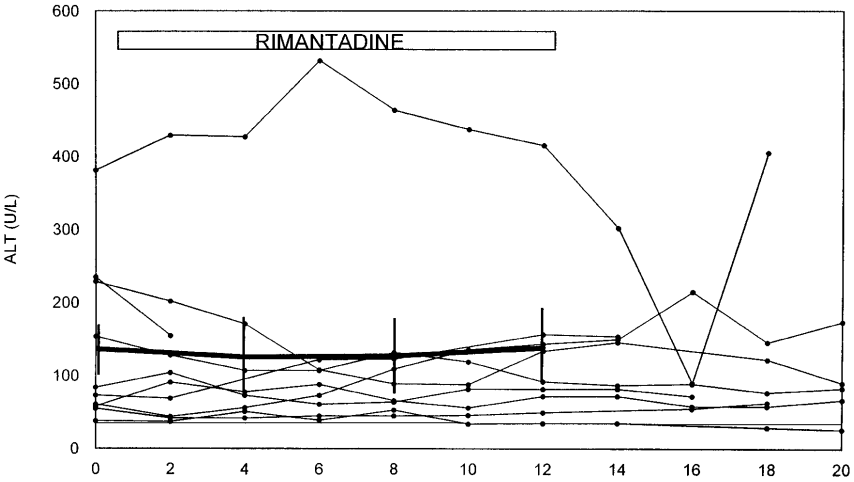

Figure 1. Mean and individual ALT levels during treatment with rimantadine in liver transplant recipients with recurrent HCV infection. Heavy line represents mean values during treatment with standard error of the mean.

resolved without drug discontinuation. No dosage reduction was performed in any patient.

Discussion

Recurrent HCV infection occurs in virtually all patients who successfully undergo transplantation with this disease. Interferon, which is the mainstay of therapy in immunocompetent patients, appears to be less effective in the post–liver transplantation setting and may be associated with an increased risk for rejection events secondary to its immunomodulatory characteristics. Therefore, a direct antiviral agent might be particularly advantageous in this patient cohort. This study was designed as an open-label pilot trial to determine if rimantadine showed direct antiviral activity against HCV in the posttransplantation setting.

The mechanism of antiviral action for rimantadine and amantadine is unclear. It appears to induce a virustatic effect early in the replication cycle, possibly by inhibiting the uncoating of influenza virions.[10] The lack of a cell culture–based system that supports HCV viral replication has limited the study of antiviral drugs in vitro. Therefore, there is only clinical evidence that this class of drug might have a beneficial effect in HCV infection, and this information is very limited at best. Only one published article described HCV antiviral activity associated with amantadine. In that study, amantadine was administered to 22 patients with HCV in whom standard interferon therapy previously failed. These patients received amantadine, 100 mg orally twice daily, for 6 months. Twenty-seven percent of the patients normalized ALT levels and lost HCV RNA.[8]

In this short-term treatment trial, we sought evidence of anti-HCV activity by accepted response criteria. Biochemical response, defined by ALT level normalization, occurred in only 1 patient, and

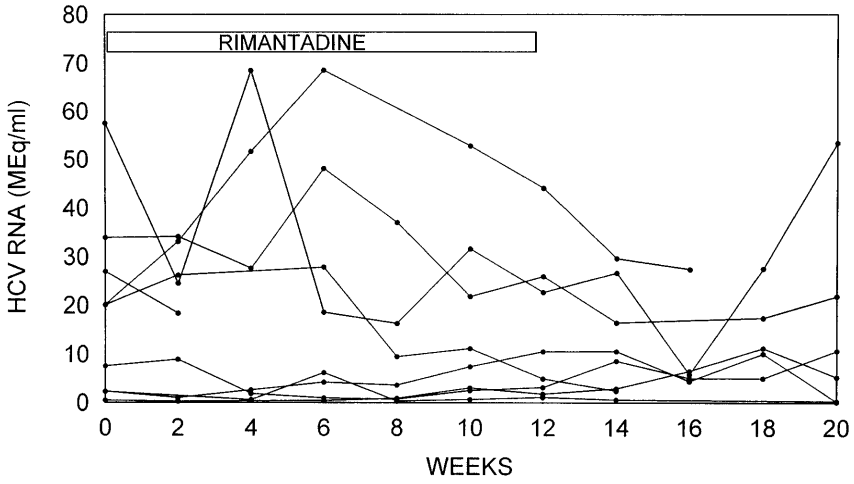

Figure 2. Individual HCV RNA titers in liver transplant recipients during and after treatment with rimantadine. Viral titers were obtained by the branched-chain method. (Quantiplex 2.0; Chiron Corp, Emeryville, CA)

this was attributed to random variation because the patient had only slight elevations of ALT level greater than the laboratory normal values before drug administration. Mean ALT levels were unchanged during treatment. Typically, treatment with interferon is associated with mean ALT level decreases during therapy. This type of response was initially used to document the efficacy of this agent before the availability of quantitative viral RNA testing.[11,12]

Serial RNA testing also failed to show evidence of antiviral activity. No patient cleared viral RNA levels to less than even the modest limits of detection (200 000 HCV Eq/mL) that characterize the branched-chain assay. Individual patients had some variability in viral titers, as shown in Figure 2. However, none showed a pattern that could reasonably be linked to the use of the experimental agent, with an early and persistent decrease during treatment and a titer increase on drug cessation. Patients with the greatest variability tended to be those who had an adjustment of their immunosuppressive regimens during the treatment period.

Although all patients had pretreatment liver biopsies performed, this protocol did not evaluate posttreatment histological changes. Therefore, we cannot exclude the possibility that rimantadine provided benefit in that area. However, the lack of ALT level improvement suggests that such improvement is unlikely.

Ribavirin is an antiviral agent that also failed to show significant activity against HCV when used as monotherapy in immunocompetent patients. However, in combination with interferon, it appears to significantly improve sustained response rates in responder patients.[13] In the posttransplantation setting, interferon monotherapy has been compared with ribavirin monotherapy, but the combination was not studied.[14] It is possible that rimantadine might also enhance interferon effects when used as a combination therapy, but that hypothesis was not tested in this study. Therefore, we conclude that rimantadine monotherapy has no role in the treatment and management of posttransplantation HCV infection. Further pilot studies may provide evidence of a role for this drug in combination with interferon or other agents.

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