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Short communication

Combination therapy with ribavirin and amantadine in renal transplant patients with chronic hepatitis C virus infection is not superior to ribavirin alone

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Abstract

Background: Standard treatment of chronic hepatitis C virus (HCV) infection based on interferon is not an option in renal transplant recipients due to the high risk of acute allograft rejection.
Objectives: To assess efficacy and tolerability of combined treatment with ribavirin and amantadine regarding viral clearance, normalization of liver enzymes, and improvement of HCV-related hepatopathy and graft nephropathy in HCV-RNA-positive renal transplant patients.
Study design: Prospective randomized controlled study comparing ribavirin, 1000 mg daily ($n = 7$), versus ribavirin, 1000 mg, in combination with amantadine, 200 mg daily ($n = 8$), for 12 months, versus no therapy (controls, $n = 26$). Results were evaluated by intention-to-treat analysis.
Results: No relevant differences among treatment groups were found regarding liver enzymes, HCV viremia, liver histology and renal parameters. However, antiviral treatment was limited by anemia, resulting in premature withdrawal from therapy and requiring substitution with recombinant erythropoietin in most patients. The best predictor for tolerability of active treatment was a creatinine clearance rate > 50 ml/min.
Conclusions: Addition of amantadine to ribavirin seems not to be superior to ribavirin monotherapy in renal transplant patients with chronic replicating HCV infection. However, this may be explained in part by the poor tolerability of both ribavirin and amantadine in patients with impaired renal function, resulting in drop-outs and subtherapeutic drug dosage.

Keywords: HCV infection; Hepatitis C; Amantadine; Ribavirin; Renal transplantation; Hepatopathy

1. Introduction

Chronic infection with hepatitis viruses continues to pose a major burden in patients on renal replacement therapy (Fehr and Ambühl, 2004). The prevalence of hepatitis C virus (HCV) infection in patients with a kidney allograft ranges from 5 to 50% (Hammoud et al., 1996). Compared to HCV-negative transplant patients survival in graft recipients with replicating HCV infection remains worse (Hanafusa et al., 1998). Similarly, graft survival is reduced in HCV-positive versus HCV-negative patients (Fabrizi et al., 2001; Periera et al., 1995).

Standard therapy regimens for HCV infection containing interferon are to be avoided in kidney transplant patients, as regular dose interferon leads to allograft rejection in about 20% of patients (Durlik et al., 1998). Ribavirin monotherapy given for 12 and 22.4 months, respectively, to renal transplant recipients with replicating HCV infection decreased liver enzyme levels but not viral load (Fontaine et al., 2004; Kamar et al., 2003). Only one study showed an improvement of hepatic lesions (Fontaine et al., 2004), the other

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reported improvement in both renal function and proteinuria (Kamar et al., 2003). The efficacy of ribavirin therapy on HCV clearance may theoretically be enhanced by addition of amantadine. Amantadine has antiviral (De Clercq, 2004) and immunomodulatory effects (Martin et al., 1999). The only study with amantadine monotherapy in a renal transplant population resulted in a significant decrease in alanine transaminase after 3 and 6 months of therapy, without changes in viremia and liver histology (Kamar et al., 2004).

Based on the available data in non-transplant patients (Brillanti et al., 2000; Mangia et al., 2001) we hypothesized that combination therapy of ribavirin and amantadine is superior to ribavirin monotherapy with regard to viral clearance, normalization of liver enzymes, and improvement of HCV-related hepatopathy and graft nephropathy in renal transplant patients with replicating HCV infection. Given the lack of valid treatment options for HCV-positive patients with a renal allograft, we performed a prospective, randomized controlled pilot study, examining the efficacy and tolerability of combined treatment with ribavirin and amantadine.

2. Methods

Previous screening with PCR of our approximately 900 renal transplant patients revealed 49 HCV-RNA-positive individuals (Fehr et al., 2003). Among those, 24 consented to a percutaneous liver biopsy and were offered to participate in the therapeutic trial described herein. Baseline patient characteristics are shown in Table 1. Fifteen patients were randomized to receive ribavirin (Copegus®, Roche, Basel, Switzerland), 1000 mg/day, either as monotherapy ($n = 7$) or in combination with amantadine sulphate (PK-Merz®, Merz, Switzerland), 200 mg/day ($n = 8$) for 12 months. Initial ribavirin dose was given adjusted according to body weight (<65 kg: 800 mg/day; >85 kg: 1200 mg/day) and creatinine clearance (CrCl: <30 ml/min: initial dose: 200 mg/day). The dose was tapered to 600 mg/day or less for hemoglobin < 10 g/dl, and was interrupted for hemoglobin < 8.5 g/dl. Initial amantadine dose was given adjusted for CrCl (80–60 ml/min: 100 mg twice daily; 60–50 ml/min: 200 and 100 mg, respectively, on alternating days; 50–30 ml/min: 100 mg once daily; 30–20 ml/min: 200 mg twice weekly; 20–10 ml/min: 100 mg thrice weekly). Recombinant human erythropoietin (rhEPO) was administered, if necessary, to maintain hemoglobin concentration > 10 g/dl.

Patients were followed clinically and by laboratory controls over 12 months after start of therapy. CrCl was calculated according to the formula of Cockcroft and Gault (1976). HBsAg, anti-HBs and anti-HCV antibodies were determined by AXSYM MEIA technique (Abbott Laboratories, Abbott Park, IL, USA). HCV-RNA was determined by Cobas Amplicor HCV Monitor 2.0 (Roche Diagnostics, Basel, Switzerland). Another liver biopsy was performed 12 months after start of therapy. Liver specimens had to be 2 cm or more in length containing at least 11 complete portal tracts to be reliable for grading and staging chronic viral hepatitis (Guido and Rugge, 2004). The modified histological activity index (MHAI) and fibrosis index were evaluated according to Ishak et al. (1995). MHAI represents the sum of the scores attributed to the necroinflammatory lesions ("interface hepatitis": 0–4, "confluent necrosis": 0–6, "focal necrosis": 0–4, "portal hepatitis": 0–4). The Ishak fibrosis score ranges from "absent" (0) to "cirrhosis" (6).

A control group of 26 patients was established from the cohort of 49 patients with documented replicating HCV infection that declined to undergo liver biopsy and/or study drug therapy.

2.1. Statistical analysis

Data are presented as mean ± standard deviation. Results were analyzed as "intention-to-treat", unless stated otherwise. Differences between groups were calculated using the Kruskall–Wallis test for non-parametric data. Within-group changes were analyzed by Wilcoxon signed-rank test for two related samples. Statistical significance was defined as P value < 0.05 (two-tailed). Statistical calculations were performed using SPSS for Windows software Version 12.0.1 (SPSS Inc., Chicago, IL).

The study protocol had been approved by the institutional review board, and all participants gave written informed consent.

3. Results

All results are summarized in Table 1. Baseline characteristics were comparable between treatment groups and controls. No significant changes in transaminase levels were detectable after treatment in both groups. Similarly, HCV replication was not significantly affected by either therapy regimen. Even in patients completing 12 months of active antiviral treatment no relevant changes in viral load were detectable (data not shown). In the ribavirin arm renal function decreased by about 10%, comparable to the course in the control group. In contrast, renal function was preserved in the combination group, especially in those patients that finished the trial on therapy (data not shown). Proteinuria was not affected by either treatment. In patients on monotherapy average MHAI and fibrosis scores were slightly improved. In the patient group undergoing combined treatment mean MHAI for inflammatory changes were identical to baseline, whereas the degree of fibrosis was slightly increased.

The main side effect from either treatment was anemia (Fig. 1A), which required substitution with rhEPO (Fig. 1B). Study medication had to be temporarily interrupted or permanently stopped due to anemia in two and three patients (after 2 and 3 months), respectively, in the ribavirin/amantadine group, and two patients were prematurely withdrawn from antiviral medication in the ribavirin group (after 1 and 3