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Impact of Liver Transplantation on the Survival of Patients Treated for Hepatorenal Syndrome Type 1

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Abstract

The development of hepatorenal syndrome type 1 (HRS1) is associated with a poor prognosis. Liver transplantation improves this prognosis, but the degree of the improvement is unclear. Most patients receive vasoconstrictors such as terlipressin before transplantation, and this may affect the posttransplant outcomes. We examined a cohort of patients with access to liver transplantation from our previously published study of terlipressin plus albumin versus albumin alone in the treatment of HRS1. The purpose of this analysis was the quantification of the survival benefits of liver transplantation for patients with HRS1. Ninety-nine patients were randomized to terlipressin or placebo. Thirty-five patients (35%) received a liver transplant. Among those receiving terlipressin plus albumin, the 180-day survival rates were 100% for transplant patients and 34% for nontransplant patients; among those receiving only albumin, the rates were 94% for transplant

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Additional Supporting Information may be found in the online version of this article.

patients and 17% for nontransplant patients. The survival rate was significantly better for those achieving a reversal of hepatorenal syndrome (HRS) versus those not achieving a reversal (47% versus 4%, $P < 0.001$), but it was significantly lower for the responders versus those undergoing liver transplantation (97%). We conclude that the use of terlipressin plus albumin has no significant impact on posttransplant survival. Liver transplantation offers a clear survival benefit to HRS1 patients regardless of the therapy that they receive or the success or failure of HRS reversal. The most likely benefit of terlipressin in patients undergoing liver transplantation for HRS1 is improved pretransplant renal function, and this should make the posttransplant management of this difficult group of patients easier. For patients not undergoing transplantation, HRS reversal with terlipressin and/or albumin improves survival.

Hepatorenal syndrome type 1 (HRS1) develops in patients with cirrhosis and ascites because systemic vasodilatation leads to underperfusion of the kidneys. As the systemic vasodilatation worsens, renal vasoconstriction occurs in response to underperfusion and leads to the development of HRS1.¹ The prognosis for patients who develop HRS1 is very poor, with most dying within a few weeks of the onset of renal failure.^{2,3} The realization that systemic vasodilatation, especially in the splanchnic bed, is responsible for renal failure has led to the therapeutic use of vasoconstrictors. Vasoconstriction increases the effective arterial blood volume and leads to better renal perfusion and the reversal of HRS1. Three controlled trials comparing terlipressin plus albumin to albumin alone have shown significantly more reversal of HRS1 in terlipressin-treated patients versus controls.⁴⁻⁶ Although all published studies and particularly randomized controlled studies have clearly shown benefits from terlipressin in terms of hepatorenal syndrome (HRS) reversal, improvements in transplant-free survival have not been consistently demonstrated.⁴⁻⁷ The reasons for the lack of impact on survival include the complex nature of the underlying disease, the effects of liver transplantation on survival, and the relatively small sample sizes of the trials in this orphan disease population.

Liver transplantation is considered the definitive therapy for HRS and leads to improvements in renal function once the underlying liver failure is solved.^{8,9} Because the development of renal failure is an independent predictor of survival, the serum creatinine level is 1 of the 3 variables used to calculate the Model for End-Stage Liver Disease (MELD) score. However, many patients with renal insufficiency who undergo transplantation have hepatorenal syndrome type 2 (HRS2) or little renal dysfunction. The outcome of HRS1 patients who undergo transplantation is less clear, and so is the impact of vasoconstrictor treatments on transplant outcomes. In addition, because the survival benefits of liver transplantation decline as the pretransplant serum creatinine level increases,¹⁰⁻¹³ it is important for us to compare patients with rapidly progressive renal failure who are treated with newer therapies but do not undergo transplantation to patients who undergo transplantation.

In our previous report,⁴ which demonstrated the significant effects of terlipressin on HRS1 reversal, no survival benefit could be seen in comparison with a placebo. However, there were 3 Russian study sites at which liver transplantation was not an option. Using only those patients who were treated in places where liver transplantation was available, we have now reexamined the results of our previous study, and our analysis is the subject of this report. The benefits of liver transplantation for patients with HRS1 are clearly shown when these patients are compared with patients who did not undergo liver transplantation in this well-defined cohort of patients and with historical controls. The impact of terlipressin/albumin use on posttransplant survival can now be ascertained because we have a control group of patients who received albumin alone and underwent liver transplantation.

Patients and Methods

Patients and Study Design

Adult subjects (≥ 18 years old) with HRS1, which was defined as a doubling of the serum creatinine level to >2.5 mg/dL in less than 2 weeks, were eligible for the study.¹⁴ The exclusion criteria and other details are provided in our previous publication.⁴ This is a subgroup analysis of all 99 patients from the United States (30 centers) and Germany (2 centers) who were treated in our prospective, randomized, double-blinded, placebo-controlled, multicenter trial. Patients from Russia were excluded because liver transplantation was not available to those individuals.

This study was approved by the institutional review boards at each site and was registered in the national database of clinical trials (ClinicalTrials.gov identifier NCT00089570). After randomization, the patients received blinded study medications: intravenous terlipressin at a dose of 1 mg every 6 hours or a matching placebo. It was also recommended that all patients receive 100 g of albumin on day 1 and 25 g daily until the end of the study. The maximum length of treatment was 14 days. Further details are provided in the original article.⁴

Study Endpoints and Statistical Analyses

All efficacy analyses were based on an intention-to-treat analysis. Transplant-free survival and overall survival were analyzed with a 2-sample log-rank test that was adjusted for baseline strata (the presence or absence of alcoholic hepatitis). A summary of product limit estimates for the survival distribution was also provided for the treatment group (Proc Lifetest, SAS Institute, Inc., Cary, NC). SAS 8.2 was used to perform all statistical analyses and to prepare summary tables and data listings.

Results

Ninety-nine patients from the United States and Germany were included in the analysis. Forty-seven patients received terlipressin, and 52 patients received a placebo. Thirty-five patients received a liver transplant, but 64 did not. There were no dual liver-kidney transplants. Table 1 lists the features of the patients who were eligible for liver transplantation in the 2 groups. Renal failure was slightly more severe in those who had received the placebo, and more of the placebo patients were on dialysis at the time of transplantation; however, none of the differences were significant.

Figure 1 shows the transplant-free survival rates for the terlipressin-treated patients and the placebo-treated patients. Although the survival rate was slightly better for those receiving terlipressin (34% versus 17% for the placebo-treated patients), the difference was not significant. Liver transplantation is the only definitive treatment for HRS1, but there are few data on the short-term survival of this group of patients. Therefore, we examined the effects of liver transplantation on patients treated with placebo and albumin who underwent transplantation, patients treated with placebo and albumin who did not undergo transplantation, and patients in a historical control group.¹⁵ As can be seen in Fig. 2, the survival of the placebo patients who did not undergo transplantation but did receive albumin was poor and differed little from the survival of the historical control group. In contrast, the survival at 180 days was excellent for those who underwent transplantation. Figure 3 presents the overall survival rates of the nontransplant patients on terlipressin plus albumin or albumin alone who achieved HRS reversal, the nontransplant patients who did not achieve HRS reversal, and the patients who underwent liver transplantation. Survival was significantly better for the HRS responders versus the nonresponders (47% versus 4% at 180 days, $P < 0.001$), but the 180-day survival rate of the HRS responders was significantly less than that of the patients who underwent transplantation (97%, $P < 0.001$). Because this trial

was designed to examine the short-term benefits of terlipressin administration on renal function, no posttransplant data on patients' renal function were collected. On the basis of previous studies, it can be assumed that some of the patients (but perhaps not all) experienced improvements in posttransplant renal function (as discussed later).

Discussion

Liver transplantation is considered the only definitive therapy for HRS because it improves survival and restores renal function. The magnitude of the survival benefit and the effects of liver transplantation in comparison with newer therapies such as terlipressin are, however, unclear. This report presents the largest published study of the impact of liver transplantation on the survival of patients with HRS1 in which a well-matched control group with the same disease severity was managed in a similar manner but did not undergo transplantation. Among those not undergoing transplantation, the 6-month survival rate was 17% in the albumin-only cohort and 34% in the terlipressin/albumin group (Fig. 1). There was no survival advantage for those who received albumin alone versus a historical cohort (Fig. 2). There was a small survival advantage for the terlipressin-treated patients, but the difference was not significant. In contrast, 94% of the patients treated with only albumin and 100% of the terlipressin-treated patients survived 6 months with liver transplantation.

Three previous reports¹⁶⁻¹⁸ have examined the effects of liver transplantation on the survival of patients with HRS. In one series, 9 patients with HRS (3 with HRS1 and 6 with HRS2) who had been treated with terlipressin and had achieved HRS reversal underwent transplantation, and their survival was compared to the survival of 27 matched controls who underwent transplantation without renal failure. The survival rates at 3 years were 100% for the patients who underwent transplantation with renal failure and 83% for the patients who underwent transplantation without renal failure; the difference was not significant.¹⁶ Restuccia et al.¹⁶ concluded that the good outcomes for those with HRS were influenced by the pre-transplant use of terlipressin and the associated improvements in renal function. Although the follow-up period of our study is only 6 months, the survival rates are similar to those reported by Restuccia et al. The excellent survival in our study, however, was not affected by whether or not the patients received terlipressin or achieved HRS reversal (4 terlipressin-treated patients and 1 albumin-treated patient with HRS reversal underwent transplantation); this suggests that transplantation (rather than the treatment) leads to good outcomes. In a second series of 32 patients with HRS1 who underwent transplantation in China, 8 (25%) died within the first month.¹⁷ The factors that were predictive of death were a MELD score > 36 and a serum sodium level < 126 mEq/L. There was no control group in this trial. In our trial, the mean MELD scores were 33 for terlipressin/albumin patients who underwent transplantation and 32 for albumin-only patients. Seven terlipressin/albumin patients and 3 albumin-only patients underwent transplantation with MELD scores > 36. Hence, according to this study, patients with HRS and high MELD scores still have an excellent short-term posttransplant prognosis. In a third series of 31 patients with HRS (type not specified), the survival of HRS patients was compared to the survival of patients who underwent transplantation at a single center during the same time period. At the end of the first year, the survival rates were 77% for those with HRS and 87% for those who underwent transplantation without HRS.¹⁸ Hence, according to the current and previous studies of patients with HRS and especially HRS1, this group has a good prognosis after liver transplantation. Perhaps more importantly, patients with HRS1 who do not undergo transplantation and do not receive terlipressin have an extremely poor prognosis, which has not changed perceptibly in the last decade (Fig. 2).

For nontransplant patients, who often have contraindications to liver transplantation (eg, alcoholic hepatitis), successful treatment with terlipressin/albumin or albumin alone predicts

not only an improvement in renal function but also improved survival (47% at 180 days); however, patients whose renal function does not improve have dismal outcomes (4% survival at 180 days, $P < 0.001$; Fig. 3). Thus, for patients who cannot receive a transplant despite the availability of transplants in their region, a response to terlipressin or other vasoconstrictors is the only opportunity for improved survival outcomes. However, despite this improvement, the survival rate of patients achieving HRS reversal was much worse than the survival rate of patients who received a liver transplant (47% versus 97%, $P < 0.001$; Fig. 3). Thus, it is unlikely that newer therapies with higher response rates (eg, terlipressin) will reduce the need for liver transplantation in the near future.

Improvements in pretransplant renal function may have some benefits in the posttransplant period. For example, the risk of toxicity from calcineurin inhibitors as well as the need for hemodialysis may be reduced.¹³ Also, if some patients could be prevented from progressing to acute renal failure, the need for dual liver-kidney transplantation might be reduced. This trial was designed to examine the effects of terlipressin on renal function over a 14-day observation period. Relapses were observed in only 1 of the 19 terlipressin responders and in only 1 of the 7 responding controls.⁴ Both patients responded to retreatment. No further relapses were observed during the following 60 days. However, once a patient underwent transplantation, his or her renal function was no longer followed in the trial. The benefits of liver transplantation on the renal function of patients with HRS are well known. In one series of patients treated with terlipressin in whom HRS was reversed before transplantation, the rates of renal insufficiency at 6 months were similar for those who did have HRS before transplantation and those who did not.¹⁶ In a second series of 32 patients with HRS1 who underwent liver transplantation, 30 recovered renal function over a median time of 24 days (range = 1-234 days). The other 2 patients died with renal insufficiency. Dialysis was required after transplantation for 8 patients.¹⁷ In a third series, renal function improved in patients with HRS (type not specified) who underwent liver transplantation. Renal function 1 year after transplantation was similar for those who did have HRS before transplantation and those who did not.¹⁸ In a fourth series, 22 patients with HRS who were on dialysis for more than 30 days and received a simultaneous liver-kidney transplant were compared to 148 HRS patients who received a liver-only transplant (80 were on dialysis for less than 30 days). Renal function was recovered in essentially all patients who received a liver-only transplant. The outcomes were similar for the 2 groups with respect to survival and the recovery of renal function.¹⁹ Liver transplantation, therefore, improves not only survival but also renal function in patients with HRS1. Current guidelines recommend that combined liver-kidney transplantation should be limited to patients with HRS who have been receiving dialysis for more than 8 weeks.²⁰

This study confirms that the prognosis is poor for patients with HRS1 despite advances in treatment and shows that liver transplantation is the definitive treatment for eligible patients. The use of vasoconstrictors such as terlipressin plus albumin improves renal function and survival in those responding to treatment who are unable to receive a transplant; however, the survival of patients who achieve HRS reversal is still much worse than the survival of those receiving a liver transplant. Further studies are needed to determine whether terlipressin and similar drugs can reduce the time in the intensive care unit and the need for renal replacement therapy before and after transplantation and diminish the need for dual-organ transplantation. These are especially important studies because renal function at the time of liver transplantation appears to be most predictive of posttransplant chronic renal failure.²¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

HRS	hepatorenal syndrome
HRS1	hepatorenal syndrome type 1
HRS2	hepatorenal syndrome type 2
MELD	Model for End-Stage Liver Disease

Figure 1. Transplant-free survival in patients receiving terlipressin plus albumin ($n = 47$) and patients receiving albumin alone ($n = 52$). The 99 patients came from 32 centers offering liver transplantation ($P = 0.40$).

Figure 2.

Cross-trial comparison of the overall survival of (-○-) albumin-only (placebo) patients who underwent liver transplantation (n = 17), (-●-) albumin-only (placebo) patients who did not undergo liver transplantation (n = 34), and (···) a historical cohort of untreated, nontransplant patients with cirrhosis after a diagnosis of HRS1. The historical control group was taken from Gines et al.¹⁵

Figure 3.

Overall survival of (—○—) transplant patients ($n = 35$), (—●—) nontransplant patients who achieved HRS reversal ($n = 17$), and (---○---) nontransplant patients who did not achieve HRS reversal ($n = 47$). The difference between the transplant group and the 2 nontransplant groups was significant ($P < 0.001$). The difference between those achieving HRS reversal and those not achieving HRS reversal was also significant ($P < 0.001$).

Table 1
Patients Who Were Eligible for Liver Transplantation (n = 99)

Parameter	Terlipressin Group (n = 47)	Placebo Group (n = 52)
Transplant patients [n (%)]	18 (38)	17 (33)
Time to transplantation (days) *	31 (1-142)	21 (5-113)
Drug exposure: doses (n)	23	19
Baseline serum creatinine level (mg/dL)	3.1	3.5
Last on-treatment serum creatinine level (mg/dL)	2.8	3.8
Dialysis before transplantation (%)	39	53
Baseline serum sodium level (mmol/L)	130	133
Last on-treatment sodium level (mmol/L)	134	135
Baseline MELD score	33	32
Last on-treatment MELD score	31	32
Living on day 180 (%)		
Transplant patients	100	94
Nontransplant patients	34	17

* The data are presented as means and ranges.