ORIGINAL ARTICLE

Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome

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ABSTRACT

BACKGROUND

The vasoconstrictor terlipressin is used for type 1 hepatorenal syndrome (HRS-1) in many parts of the world and is part of the clinical practice guidelines in Europe.

METHODS

We conducted a phase 3 trial to confirm the efficacy and safety of terlipressin plus albumin in adults with HRS-1. The patients were randomly assigned in a 2:1 ratio to receive terlipressin or placebo for up to 14 days; in both groups, concomitant use of albumin was strongly recommended. The primary end point was verified reversal of HRS, defined as two consecutive serum creatinine measurements of 1.5 mg per deciliter or less at least 2 hours apart and survival without renal-replacement therapy for at least 10 days after the completion of treatment. Four prespecified secondary end points were analyzed with the Hochberg procedure to account for multiple comparisons.

RESULTS

A total of 300 patients underwent randomization — 199 were assigned to the terlipressin group and 101 to the placebo group. Verified reversal of HRS was reported in 63 patients (32%) in the terlipressin group and 17 patients (17%) in the placebo group ($P=0.006$). With respect to the prespecified secondary end points, HRS reversal, defined as any serum creatinine level of 1.5 mg per deciliter or less during the first 14 days, was reported in 78 patients (39%) in the terlipressin group and 18 (18%) in the placebo group ($P<0.001$); HRS reversal without renal-replacement therapy by day 30, in 68 (34%) and 17 (17%), respectively ($P=0.001$); HRS reversal among patients with systemic inflammatory response syndrome (84 patients in the terlipressin group and 48 patients in the placebo group), in 31 (37%) and 3 (6%), respectively ($P<0.001$); and verified reversal of HRS without recurrence by day 30, in 52 (26%) and 17 (17%), respectively ($P=0.08$). At day 90, liver transplantations had been performed in 46 patients (23%) in the terlipressin group and 29 patients (29%) in the placebo group, and death occurred in 101 (51%) and 45 (45%), respectively. More adverse events, including abdominal pain, nausea, diarrhea, and respiratory failure, occurred with terlipressin than with placebo. Death within 90 days due to respiratory disorders occurred in 22 patients (11%) in the terlipressin group and 2 patients (2%) in the placebo group.

CONCLUSIONS

In this trial involving adults with cirrhosis and HRS-1, terlipressin was more effective than placebo in improving renal function but was associated with serious adverse events, including respiratory failure. (Funded by Mallinckrodt Pharmaceuticals; CONFIRM ClinicalTrials.gov number, NCT02770716.)

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Type 1 hepatorenal syndrome (HRS-1) is a condition of rapidly progressing kidney failure that occurs in patients with decompensated cirrhosis and ascites.[1,2] Untreated HRS-1 is often fatal, with a median duration of survival of weeks to months.[3,4] Pharmacotherapy with vasopressors may reverse the hemodynamic abnormalities associated with advanced cirrhosis and improve renal perfusion and function in patients with HRS-1.[4]

Terlipressin is a synthetic vasopressin analogue with vasoconstrictor activity in the splanchnic and systemic vasculature.[5] This activity results in decreased portal blood inflow and reduced portal hypertension, the main cause of the hemodynamic abnormalities associated with advanced cirrhosis. The consequent redistribution of circulatory volume from the splanchnic to the systemic circulation improves systemic hemodynamics and increases renal perfusion pressure.[6,7] The increased effective arterial volume also decreases compensatory renal and systemic vasoconstrictor activities, further improving renal hemodynamics in these patients.[3] The efficacy and safety of terlipressin in patients with HRS-1 have been evaluated in previous randomized, multicenter, placebo-controlled trials of varying sizes.[8-10] Terlipressin is used for HRS-1 in many parts of the world[11] and is part of the Clinical Practice Guidelines in Europe.[12] The main objective of the CONFIRM Study was to confirm the efficacy and safety of terlipressin plus albumin, as compared with placebo plus albumin, in adults with cirrhosis and HRS-1.

Methods

Trial Design

The protocol (available with the full text of this article at NEJM.org) for this randomized, double-blind, placebo-controlled trial was developed under a special protocol assessment agreement with the Food and Drug Administration as a phase 3 registration trial[13] and was approved by the research ethics board at each participating institution.[14] The trial was designed by the sponsor, together with the second author. All the trial investigators gathered and vouch for the data. The first author wrote the first and subsequent drafts of the manuscript. A statistician (one of the authors) employed by the sponsor analyzed the data and vouches for the analysis. All the authors had access to the data and vouch for the fidelity of the trial to the protocol.

The patients underwent an in-hospital screening period of a minimum of 48 hours to establish the diagnosis of HRS-1 (Fig. S1 in the Supplementary Appendix, available at NEJM.org), after which eligibility was confirmed and baseline assessments were made. The serum creatinine level was measured within 8 hours before the first dose of terlipressin or placebo; thereafter, terlipressin or placebo was administered every 6 hours, and this regimen was continued either until 24 hours after a serum creatinine level of 1.5 mg per deciliter (133 μmol per liter) or less was obtained in two consecutive measurements or until day 14. If on day 4 (after a minimum of 10 doses), the serum creatinine level was at or above the baseline level, the assigned regimen was discontinued. The assigned regimen was also discontinued if a patient received renal-replacement therapy or therapy with another vasopressor or underwent liver transplantation or transjugular intrahepatic portosystemic shunt placement. After completion of the terlipressin or placebo regimen, patients were assessed between days 20 and 40, between days 46 and 74, and between days 76 and 104. Among the patients who were discharged before completing their assigned regimen or who withdrew consent, no further information was collected except on mortality. The patients who were discharged after meeting the criteria for clinical success were monitored for HRS recurrence.

Patients

Eligible patients had HRS-1, cirrhosis, ascites, and rapidly progressive kidney failure, with a doubling of the serum creatinine level to at least 2.25 mg per deciliter (199 μmol per liter) within 14 days before randomization. In patients who had an increasing serum creatinine level during the prescreening period, a nomogram was used to determine whether the slope of the patient's serum creatinine levels was consistent with a trajectory likely to be representative of at least a doubling within 2 weeks.[13] Patients were excluded if they had a sustained reduction in the serum creatinine level of more than 20% or a decrease to below 2.25 mg per deciliter at least 48 hours after diuretic withdrawal and albumin infusions. Patients in whom treatment with midodrine and octreotide was discontinued before randomization were eligible for enrollment.

Major exclusion criteria were a serum creatinine level of greater than 7.0 mg per deciliter (619 μmol per liter), one or more large-volume paracenteses of 4 liters or more within 2 days before randomization, the presence of sepsis or uncontrolled bacterial infection (or both) for which antibiotic treatment had been administered for less than 2 days, or severe cardiovascular disease or recent (within 4 weeks before randomization) renal-replacement therapy. Additional details are provided in the Supplementary Appendix. Written informed consent was obtained from all the patients or their legally authorized representatives.

RANDOMIZATION AND CLINICAL REGIMEN

Patients were randomly assigned in a 2:1 ratio to receive terlipressin plus albumin or placebo plus albumin; randomization was performed with the use of independently generated codes. Stratification factors were a qualifying serum creatinine level (<3.4 mg per deciliter [301 μmol per liter] or ≥3.4 mg per deciliter) and preenrollment large-volume paracentesis (at least one event of ≤4 liters within 3 to 14 days before randomization).

Patients received terlipressin or placebo in a blinded manner; 1 mg of terlipressin or placebo was administered intravenously over 2 minutes every 5.5 to 6.5 hours. It was strongly recommended that all patients receive albumin (1 g per kilogram of body weight to a maximum of 100 g on day 1 and 20 to 40 g per day thereafter).[1,15] On day 4, patients with a serum creatinine level that had decreased by less than 30% from the baseline level after a minimum of 10 doses of terlipressin or placebo could receive 2 mg every 6 hours, except in those with coronary artery disease, circulatory overload, pulmonary edema, or bronchospasm. If the regimen was interrupted because of adverse events, resumption of the dosing schedule was permitted except in patients who had cardiac or mesenteric ischemia, in whom the regimen was permanently discontinued.

EFFICACY END POINTS

The primary efficacy end point was verified reversal of HRS, defined as two consecutive serum creatinine measurements of 1.5 mg per deciliter or less at least 2 hours apart up to day 14 and survival without renal-replacement therapy for at least an additional 10 days. Clinical failure was classified in patients if they received renal-replacement therapy, underwent transjugular intrahepatic portosystemic shunt placement, or received open-label vasopressor therapy before day 14; if the serum creatinine level had not improved by day 4; or if the serum creatinine level had not decreased to 1.5 mg per deciliter or less by day 14. The assigned regimen was discontinued if a patient had clinical failure or underwent liver transplantation. Liver transplantation and death were considered to be competing events when they occurred before a patient could be evaluated for clinical success or failure (nine patients in the terlipressin group and two patients in the placebo group underwent liver transplantation before they could be evaluated, and two patients in the terlipressin group died before they could be evaluated). Patients were considered to be unclassifiable with respect to the primary end point if they had not had a competing event and did not meet the criteria for clinical success or failure or if data on the serum creatinine level were not available because of hospital discharge, withdrawal of consent, or another reason during the planned treatment period (up to 14 days) and the day after; the results for these patients were imputed with the use of multiple imputation (additional details are provided below and in the Supplementary Appendix).

Four prespecified secondary efficacy end points were adjusted for multiple comparisons: HRS reversal, defined as a serum creatinine level of 1.5 mg per deciliter or less; durability of HRS reversal, defined as HRS reversal without renal-replacement therapy to day 30; HRS reversal among patients with systemic inflammatory response syndrome; and verified reversal of HRS without recurrence of HRS by day 30. The same imputation method used in the analysis of the primary end point was applied to the secondary end points. Additional details of the end-point definitions are provided in Table S1.

SAFETY

Data on nonserious adverse events were collected up to 7 days after the end of the treatment period, and data on serious adverse events were collected up to 30 days after the end of the treatment period. Mortality was documented for up to 90 days after the first dose of terlipressin or placebo.

STATISTICAL ANALYSIS

Efficacy analyses were performed in the intention-to-treat population, which comprised all patients who underwent randomization. The sample size

for the analysis of the primary efficacy end point was calculated on the basis of pooled estimates of HRS reversal (8.4% with terlipressin and 12.5% with placebo) from two previous trials of terlipressin for HRS-1.[8,10] With a randomization ratio of 2:1 between terlipressin and placebo and an interim analysis after 50% of the patients completed the planned treatment period of up to 14 days or were discharged, a sample size of 300 patients was expected to provide 90% power to detect a significant difference between the groups with respect to the primary efficacy end point.

In the prespecified analysis, clinical success with respect to the primary end point required improvement in the serum creatinine level while receiving terlipressin or placebo, and clinical failure was classified in all patients who discontinued their assigned regimen before meeting the criteria for clinical success. In accordance with the intention-to-treat principle, we modified the definition of clinical success so that it was not required to continue receiving terlipressin or placebo in order to achieve clinical success. For the patients who withdrew from the trial or were discharged and did not have available data on the serum creatinine level through day 15, we used multiple imputation to account for missing end-point data. Multiple imputation was performed with the use of an imputation model that included seven variables (additional details are provided in the Supplementary Appendix). In the analysis of the primary and secondary end points, the PROC MI, PROC SURVEYFREQ, PROC GENMOD, and PROC MIANALYZE procedures in SAS software, version 4 (SAS Institute), were used to generate and combine the results on the basis of imputations.

A Hochberg procedure was used to adjust for multiple testing of the four secondary end points. A detailed statistical analysis plan is provided in the protocol.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Terlipressin (N=199)	Placebo (N=101)
Age — yr	54.0±11.3	53.6±11.8
Male sex — no. (%)	120 (60)	59 (58)
Cause of liver cirrhosis — no. (%)		
Alcohol use	134 (67)	67 (66)
Nonalcoholic steatohepatitis	42 (21)	24 (24)
Viral hepatitis	35 (18)	8 (8)
Autoimmune hepatitis	10 (5)	5 (5)
Primary biliary cirrhosis	5 (3)	3 (3)
Other cause or cryptogenic liver disease	15 (8)	8 (8)
Alcoholic hepatitis — no. (%)	81 (41)	39 (39)
Systemic inflammatory response syndrome — no. (%)†	84 (42)	48 (48)
Mean arterial pressure — mm Hg	78.7±12.1	77.5±9.4
Serum sodium level — mmol/liter	133.1±5.6	133.3±5.5
Serum creatinine level — mg/dl	3.5±1.0	3.5±1.1
Total bilirubin level — mg/dl	13.1±13.5	15.0±15.6
Albumin level — g/dl	3.7±0.7	4.0±2.6
Child–Pugh score‡	10.0±1.85	10.2±1.89
MELD score§	32.7±6.6	33.1±6.2

* Plus–minus values are means ±SD. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4.

† Systemic inflammatory response syndrome is diagnosed when two or more of the following criteria are met: body temperature lower than 36°C or higher than 38°C; heart rate greater than 90 beats per minute; respiratory rate greater than 20 breaths per minute or partial pressure of arterial carbon dioxide lower than 4.3 kPa (32 mm Hg); white-cell count lower than 4000 cells per cubic millimeter or higher than 12,000 cells per cubic millimeter; or the presence of more than 10% immature neutrophils (band forms).

‡ The Child–Pugh score is based on five clinical measures of liver function (total bilirubin level, serum albumin level, prothrombin time, ascites, and hepatic encephalopathy, with each measure graded according to severity); scores range from 5 to 15, with higher scores indicating more advanced liver disease.

§ The Model of End-Stage Liver Disease (MELD) score is based on the international normalized ratio for prothrombin time (INR) and serum bilirubin and creatinine levels and is calculated as follows: [3.78×ln(serum bilirubin in milligrams per deciliter)]+[11.2×ln(INR)]+[9.57×ln(serum creatinine in milligrams per deciliter)]+6.43, where ln is natural log. Scores range from 6 to 40, with higher scores indicating more severe disease, and have been shown to be predictive of survival in a wide variety of patients with cirrhosis.

RESULTS

PATIENTS

The trial was conducted between July 13, 2016, and July 24, 2019, at 60 sites in the United States and Canada. A total of 300 patients were randomly assigned to receive terlipressin (199 patients) or placebo (101 patients). The clinical and demographic characteristics of the patients at baseline were generally well balanced between the trial groups (Table 1 and Table S2). Concomitant albumin was administered in 165 patients (83%) in the terlipressin group (mean [±SD] total dose per person, 199.4±146.8 g over a median of 5.0 days) and 92 patients (91%) in the placebo group (mean total dose, 239.5±183.6 g over a median of 5.5 days). A total of 121 patients (61%) in the terlipressin group and 61

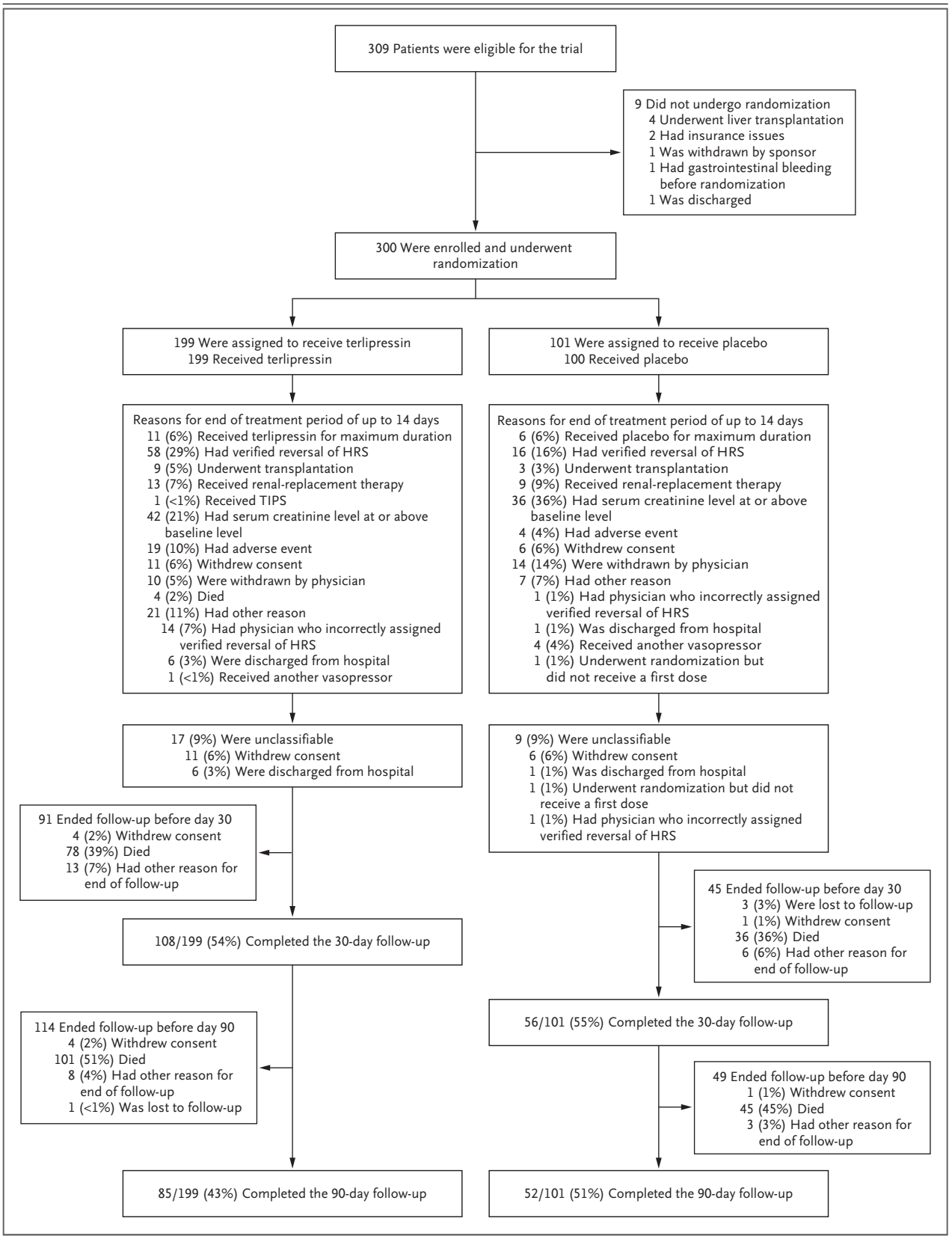

Figure 1 (facing page). Screening, Randomization, and Follow-up.

The categories of "withdrew consent" and "had other reason for end of follow-up" are not cumulative; the categories of "lost to follow-up" and "died" are cumulative. Some patients had more than one reason for ending follow-up. Among the reasons for the end of the treatment period of up to 14 days, the category of "died" in the terlipressin group applies to 4 patients who died during the time they were receiving the drug. A total of 9 patients in the terlipressin group and 1 patient in the placebo group died during the on-treatment period (defined as the period from the first dose up to 24 hours after discontinuation of the regimen). The patients who died within 24 hours after discontinuation of the regimen were included in the category "had other reason." HRS denotes hepatorenal syndrome, and TIPS transjugular intrahepatic portosystemic shunt.

patients (60%) in the placebo group had previously received midodrine and octreotide. Details regarding the screening, randomization, and follow-up of the patients are provided in Figure 1 and Figure S2.

EFFICACY END POINTS

The percentage of patients who had verified reversal of HRS (the primary end point) was significantly higher in the terlipressin group than in the placebo group (32% [63 patients] vs. 17% [17 patients]; P=0.006) (Table 2); 17 patients in the terlipressin group and 9 patients in the placebo group were considered to be unclassifiable with respect to the primary end point (Fig. 1 and Fig. S2). The reasons for failure to have verified reversal of HRS are detailed in Table S3. Three of the four secondary end points that were included in the Hochberg procedure to adjust for multiple testing were statistically significant (Table 2); the reasons for failure with respect to the secondary end points are detailed in Table S4. The results with respect to the additional secondary end points and other clinical events are reported in Table 3 and Table S5. Figure S3 shows the cumulative numbers of patients who had verified reversal of HRS and HRS reversal, respectively. The results of the prespecified analysis without multiple imputation are reported in Figure S4. Among 58 patients in the terlipressin group who had verified reversal of HRS and completed 30 days of follow-up, 10 (17%) had recurrence of HRS.

Over a mean duration of follow-up of 55.3 days, 46 patients (23%) in the terlipressin group received a liver transplant. In the placebo group, 29 patients (29%) received a liver transplant over a mean duration of follow-up of 56.1 days (Fig. S5 and Table S6). Overall or transplantation-free survival up to 90 days did not differ significantly between the two groups (Fig. S6). Other results, including Model of End-Stage Liver Disease (MELD) score, serum albumin level, and mean arterial pressure, during the treatment period are reported in Figures S7 to S9. The results of post hoc exploratory analyses of baseline variables associated with HRS reversal are reported in Figures S10 to S12. Other clinical information is provided in Table S7, and the results of other efficacy end points are reported in Table S8.

By day 90, death occurred in 101 patients (51%) in the terlipressin group and in 45 patients (45%) in the placebo group (difference, 6 percentage points; 95% confidence interval [CI], −6 to 18).

SAFETY

The safety population included all the patients who underwent randomization and received at least one dose of terlipressin or placebo. One patient in the placebo group did not receive a first dose, and 1 patient who had been assigned to receive placebo inadvertently received one dose of terlipressin and was therefore assigned to the terlipressin group in the safety population.

Adverse events of any severity, including serious adverse events, were reported in 176 of 200 patients (88%) in the terlipressin group and 88 of 99 patients (89%) in the placebo group (Table 4). The most frequently reported adverse events in the overall safety population (299 patients) were abdominal pain (45 patients [15%]), nausea (42 patients [14%]), diarrhea (33 patients [11%]), hepatic encephalopathy (33 patients [11%]), and dyspnea (30 patients [10%]) (Table S9). The percentage of patients who had abdominal pain, nausea, diarrhea, or respiratory failure was higher in the terlipressin group than in the placebo group (14% [28 patients] vs. 5% [5 patients]). The percentage of patients who had dose interruptions related to adverse events was similar in the two groups (7% in each group), whereas the percentage of patients who had permanent discontinuations of the assigned regimen owing to adverse events was higher in the terlipressin group than in the placebo group (12% [24 pa-

Table 2. Primary and Four Secondary End Points Included in Multiplicity Adjustment.*

End Point	Terlipressin	Placebo	P Value
	number/total number of patients (percent)		
Primary end point of verified reversal of HRS†			0.006
Clinical success	63/199 (32)	17/101 (17)	
Clinical failure	121/199 (61)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	
Secondary end points included in multiplicity adjustment			
HRS reversal§			<0.001
Clinical success	78/199 (39)	18/101 (18)	
Clinical failure	105/199 (53)	79/101 (78)	
Competing event‡			
Liver transplantation	11/199 (6)	4/101 (4)	
Death	5/199 (3)	0/101	
HRS reversal with no renal-replacement therapy through 30 days			0.001
Clinical success	68/199 (34)	17/101 (17)	
Clinical failure	116/199 (58)	80/101 (79)	
Competing event‡			
Liver transplantation	10/199 (5)	3/101 (3)	
Death	5/199 (3)	0/101	
HRS reversal in patients with systemic inflammatory response syndrome			<0.001
Clinical success	31/84 (37)	3/48 (6)	
Clinical failure	45/84 (54)	43/48 (90)	
Competing event‡			
Liver transplantation	4/84 (5)	1/48 (2)	
Death	5/84 (6)	0/48	
Verified reversal of HRS with no recurrence through 30 days			0.08
Clinical success	52/199 (26)	17/101 (17)	
Clinical failure	131/199 (66)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	

* Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomization. Because of multiple imputation, the total number of patients in a trial group who had clinical success, clinical failure, or a competing event with respect to each end point is either 1 less or 1 greater than the total number of patients listed in that trial group. The numbers imputed for the primary end point of verified hepatorenal syndrome (HRS) reversal were 17 in the terlipressin group and 9 in the placebo group; for HRS reversal, 16 and 8, respectively; for HRS reversal with no renal-replacement therapy through 30 days, 6 and 6, respectively; for HRS reversal in patients with systemic inflammatory response syndrome, 8 and 3, respectively; and for verified reversal of HRS with no recurrence through 30 days, 17 and 9, respectively.

† Verified reversal of HRS was defined as two consecutive serum creatinine measurements of 1.5 mg per deciliter (133 μmol per liter) or less at least 2 hours apart and survival without renal-replacement therapy for at least 10 days.

‡ Competing events included deaths or liver transplantations that occurred before the patient met the criteria for clinical success or failure. The reported numbers of competing events involving deaths and liver transplantations include outcomes that were assigned on the basis of multiple imputation.

§ HRS reversal was defined as any serum creatinine level of 1.5 mg per deciliter or less while receiving terlipressin or placebo.

tients] vs. 5% [5 patients]) (Table S10a). A total of 9 patients (4%) in the terlipressin group and 1 patient (1%) in the placebo group died during the on-treatment period (defined as the period from the initial dose to 24 hours after discontinuation of the regimen). Four patients in the terlipressin group died during the time they were receiving the drug; 5 other patients in the terlipressin group and 1 patient in the placebo group died within 24 hours after discontinuation of the regimen. The most common cause of death while receiving terlipressin or placebo was respiratory failure (6 patients [3%] in the terlipressin group and 0 patients in the placebo group), whereas the most common causes of death up to 90 days were hepatobiliary disorders (45 patients [22%] in the terlipressin group vs. 27 patients [27%] in the placebo group), respiratory disorders (22 [11%] vs. 2 [2%]), and infections (14 [7%] vs. 3 [3%]). All adverse events leading to death by day 14 are reported in Table S11, and adverse events leading to death up to 90 days are reported in Table S10b.

Table 3. Additional Secondary End Points Assessed at Days 14, 30, 60, and 90.*

End Point	Terlipressin (N=199)	Placebo (N=101)
	number of patients (percent)	
Received renal-replacement therapy		
Day 14	45 (23)	35 (35)
Day 30	51 (26)	36 (36)
Day 60	56 (28)	38 (38)
Day 90	58 (29)	39 (39)
Underwent liver transplantation		
Day 14	19 (10)	15 (15)
Day 30	32 (16)	22 (22)
Day 60	43 (22)	28 (28)
Day 90	46 (23)	29 (29)
Died		
Day 14	53 (27)	24 (24)
Day 30	78 (39)	36 (36)
Day 60	91 (46)	41 (41)
Day 90	101 (51)	45 (45)

* The number of deaths or liver transplantations up to day 30 includes those classified as competing events and those that occurred after a patient met the criteria for clinical success or failure.

DISCUSSION

In this multicenter, double-blind, randomized, controlled trial of terlipressin for the treatment of HRS-1, the percentage of patients who had verified reversal of HRS was significantly higher with terlipressin than with placebo. The primary end point in the CONFIRM Study consisted of three components (two consecutive serum creatinine measurements of ≤1.5 mg per deciliter at least 2 hours apart by day 14, absence of renal-replacement therapy for at least 10 days, and survival for at least 10 days). Combined, these three components provided a clinically meaningful measure of efficacy in improving kidney function and initial survival for 10 days after completion of treatment. The efficacy results were similar to those of trials from Europe[9] and North America.[8,10] The durability of HRS reversal with terlipressin also persisted to day 30 without the use of renal-replacement therapy; this is a clinically relevant observation because renal-replacement therapy poses many challenges for patients with advanced cirrhosis.[16] However, the reversal of HRS with terlipressin did not improve 90-day survival as compared with placebo (101 patients [51%]) vs. 45 patients [45%]; difference, 6 percentage points, 95% CI, −6 to 18). Patients in the terlipressin group were more likely to have respiratory failure and to die from respiratory disorders within 90 days after the first dose (22 patients [11%] vs. 2 patients [2%]), which probably contributed to the numerical difference in mortality. Although terlipressin improves kidney function, patients with advanced liver disease may nonetheless continue to have other complications of decompensated cirrhosis unrelated to HRS-1 and die from these complications.[17,18] This state of decompensation can be corrected only with liver transplantation. The percentage of patients who received a liver transplant within 90 days after the first dose was lower in the terlipressin group than in the placebo group (23% vs. 29%) despite there being no difference in MELD score between the two groups during the treatment period. MELD scores at the time of transplantation were not collected; therefore, it is not possible to determine whether a terlipressin-related change in MELD score had an effect on transplantation priority. It is possible that

Table 4. Adverse Events in the Safety Population.*

Event	Terlipressin (N = 200)	Placebo (N = 99)
	number of patients (percent)	
Adverse events of any grade†	176 (88)	88 (89)
Adverse events leading to discontinuation of the trial regimen	24 (12)	5 (5)
Serious adverse events with an incidence of ≥3% in either trial group‡		
Any	130 (65)	60 (61)
Cardiac disorders	8 (4)	6 (6)
Atrial fibrillation	1 (<1)	3 (3)
Gastrointestinal disorders	30 (15)	6 (6)
Abdominal pain	10 (5)	1 (1)
Gastrointestinal hemorrhage	8 (4)	0
General disorders and administration-site conditions	11 (6)	6 (6)
Multiple organ dysfunction syndrome	9 (4)	3 (3)
Hepatobiliary disorders	37 (18)	29 (29)
Chronic hepatic failure	9 (4)	8 (8)
Alcoholic cirrhosis	4 (2)	3 (3)
Hepatic cirrhosis	6 (3)	2 (2)
Hepatic failure	9 (4)	10 (10)
Worsening of HRS	3 (2)	3 (3)
Infections and infestations	19 (10)	5 (5)
Pneumonia	4 (2)	3 (3)
Sepsis	9 (4)	0
Nervous system disorders	13 (6)	3 (3)
Hepatic encephalopathy	9 (4)	3 (3)
Respiratory, thoracic, and mediastinal disorders§	33 (16)	8 (8)
Acute respiratory failure	8 (4)	2 (2)
Respiratory failure	20 (10)	3 (3)
Vascular disorders	10 (5)	4 (4)
Shock	5 (2)	3 (3)

* The safety population included all patients who underwent randomization and received at least one dose of terlipressin or placebo. For each event category, the patients were counted once even if they had multiple events in that category. One patient in the placebo group did not receive a first dose, and one patient who had been assigned to receive placebo inadvertently received one dose of terlipressin and was therefore assigned to the terlipressin group in the safety analysis.

† The numbers of events include those that occurred up to 7 days after the end of the treatment period.

‡ The numbers of events include those that occurred up to 30 days after the end of the treatment period.

§ The numbers reported for acute respiratory failure or respiratory failure are for patients with the condition as coded by the investigator; there is no overlap.

respiratory complications and sepsis or septic shock in the terlipressin group could have prevented liver transplantation.

The efficacy of terlipressin, as compared with placebo, in reversing HRS-1 was more pronounced among the subgroup of patients with systemic inflammatory response syndrome. Inflammatory cytokines have been implicated in the pathogenesis of HRS-1.[19,20] It has been postulated that terlipressin, by reducing portal pressure, may lead to a decrease in the extent of bacterial translocation across the gut wall and a consequent reduction in endotoxemia and proinflammatory cytokine production in patients with decompensated cirrhosis, changes that would facilitate the response to the hemodynamic effects of terlipressin.[21,22]

Among 58 patients in the terlipressin group who had verified reversal of HRS and completed 30 days of follow-up, 10 (17%) had recurrence of HRS, a percentage similar to that reported in the literature.[23] Terlipressin addresses the hemodynamic abnormalities behind HRS-1 but does not eliminate the clinical milieu of advanced cirrhosis from which the syndrome arises.

Overall, the results of the CONFIRM Study are in accordance with the data from previous clinical trials that provided evidence that terlipressin improves kidney function in patients with HRS-1.[4,8,10,24-27] Liver transplantation, which eliminates end-stage liver disease,[15,28] remains the only curative treatment for HRS-1. However, the majority of patients with HRS-1 do not have access to a timely liver transplantation, and alternative vasoconstrictor pharmacotherapies either have not been rigorously assessed in large clinical trials or have been shown to be ineffective.[24,29,30]

The incidence of serious adverse events was higher in the terlipressin group than in the placebo group. Abdominal pain, skin discoloration, intestinal ischemia, cardiac ischemia, cyanosis, bradycardia, and diarrhea are well-recognized potential adverse effects of terlipressin. The incidences of respiratory failure and acute respiratory failure were higher in the terlipressin group than in the placebo group, a finding that is possibly related to the known cardiovascular and pulmonary effects of terlipressin.[31-34] Terlipressin should be used with caution in patients who have the most advanced liver disease. Death within 90 days due to respiratory disorders oc-

curred in 11% of patients in the terlipressin group, as compared with 2% of patients in the placebo group.

Our trial has some limitations. The trial was not powered to assess the between-group difference in survival. A detailed follow-up beyond 90 days that included an assessment of prespecified outcomes after liver transplantation was not performed.

In the CONFIRM trial, the use of terlipressin plus albumin was more efficacious than placebo plus albumin in producing verified reversal of HRS in patients with decompensated cirrhosis and HRS-1. Terlipressin was associated with serious adverse events, including respiratory failure.

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APPENDIX

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