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ORIGINAL ARTICLE

Reduction in acute kidney injury stage predicts survival in patients with type-1 hepatorenal syndrome

Florence Wong[1], Thomas D. Boyer[2,†], Arun J. Sanyal[3], Stephen C. Pappas[4], Shannon Escalante[5] and Khurram Jamil[6]

[1]Department of Medicine, Division of Gastroenterology, University of Toronto, Toronto, ON, Canada, [2]Department of Medicine, University of Arizona, Tucson, AZ, USA, [3]Gastroenterology, Virginia Commonwealth University, Richmond, VA, USA, [4]Scientific Affairs, Orphan Therapeutics, Lebanon, NJ, USA, [5]Biometrics, Mallinckrodt Pharmaceuticals, Bedminister, NJ, USA and [6]Scientific Affairs, Mallinckrodt Pharmaceuticals, Bedminster, NJ, USA

Correspondence and offprint requests to: Florence Wong; E-mail: florence.wong@utoronto.ca
[†]Deceased.

ABSTRACT

Background. Hepatorenal syndrome type 1 (HRS-1), a form of acute kidney injury (AKI) in cirrhosis, has a median survival of days to weeks if untreated. The impact of reduction in AKI stage on overall survival in cirrhosis, independent of HRS reversal, is unclear.

Methods. The Randomized, placEbo-controlled, double-blind study to confirm the reVERSal of HRS-1 with terlipressin study assessed terlipressin versus placebo, both with albumin, as treatment for HRS-1 for ≤14 days. Renal dysfunction severity was categorized by AKI stage at enrollment. Baseline patient characteristics were evaluated as predictors of AKI improvement using a multivariate model; the association between AKI stage reduction and 90-day survival was assessed using linear regression.

Results. A total of 184 patients (terlipressin: $n = 91$; placebo: $n = 93$) with similar numbers in AKI Stages 1–3 (terlipressin/placebo, Stage 1: $n = 25/26$; Stage 2: $n = 35/33$; Stage 3: $n = 31/34$) were included. Predictors of AKI improvement were absence of alcoholic hepatitis, baseline serum creatinine and male gender. Overall survival was not significantly different across AKI stages (range 53–65%). In patients with no AKI worsening, 90-day survival was consistently better when AKI improved independent of HRS reversal, regardless of the initial AKI stage, with patients with Stage 1 at initial diagnosis achieving the greatest clinical benefit. A significant association was observed between AKI reduction and overall 90-day survival ($P = 0.0022$).

Conclusions. A reduction in AKI stage, independent of HRS reversal, was sufficient to improve overall survival in patients with HRS-1. The goal for HRS-1 treatment should be less stringent than absolute HRS reversal.

Keywords: acute kidney injury, hepatorenal syndrome type 1, survival, terlipressin

INTRODUCTION

Acute kidney injury (AKI) in patients with advanced cirrhosis has a significant, negative impact on patient outcome [1, 2]. Until AKI was defined recently for patients with cirrhosis (Table 1) [3], the presence of acute renal dysfunction was almost synonymous with the occurrence of hepatorenal syndrome type 1 (HRS-1), which is associated with a median survival of days to weeks when left untreated [4]. However, trivial acute increases in serum creatinine (SCr) in advanced cirrhosis, without reaching the threshold required for HRS-1 diagnosis, can also lead to a progressively worsening prognosis [5, 6]. The International Club of Ascites (ICA), which is responsible for defining the diagnostic criteria of AKI in cirrhosis, also set criteria for diagnosing various AKI stages to describe the severity of AKI episodes [2]. AKI progression to a higher stage signals a worsening prognosis, with an exponential increase in patient mortality [5, 7]. The corollary from this observation is that positive response to AKI treatment should lead to a reduction in AKI stage associated with improvement in patient survival. However, data on the correlation of renal function improvement or reduction in AKI stage with survival are limited.

Terlipressin, a systemic vasoconstrictor, has been used widely in Europe and Asia for treatment of patients with HRS-1 [8–10]. Meta-analyses have shown that terlipressin plus albumin is more effective in improving renal function in patients with HRS-1 compared with albumin alone [11, 12]. Whether renal function improvement and AKI stage reduction following terlipressin use in HRS-1 are associated with improved survival is unknown.

This analysis evaluates the impact of a reduction in AKI stage on survival in the Randomized, placEbo-controlled, double-blind study to confirm the reVERSal of HRS-1 with

Table 1. Diagnostic criteria and staging of AKI in cirrhosis

Parameter	Definition
Baseline SCr	Stable SCr ≤3 months If one or more SCr within the previous 3 months is available, use stable SCr closest to the admission SCr If no previous SCr is available, use the admission SCr
AKI definition	↑ in SCr ≥26.5 μmol/L (≥0.3 mg/dL) in ≤48 h or ↑ in SCr ≥50% from baseline
AKI staging	Stage 1: ↑ SCr ≥26.5 μmol/L (≥0.3 mg/dL) or ↑ SCr ≥1.5- to 2.0-fold from baseline Stage 2: ↑ SCr >2.0- to 3.0-fold from baseline Stage 3: ↑ SCr >3.0-fold from baseline or SCr ≥353.6 μmol/L (≥4.0 mg/dL) with an acute ↑ of ≥26.5 μmol/L (≥0.3 mg/dL) or initiation of RRT

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terlipressin (REVERSE; NCT01143246), a large, prospective, randomized placebo-controlled study of terlipressin plus albumin versus albumin alone in cirrhotic patients with HRS-1 [13].

MATERIALS AND METHODS

The REVERSE trial, a phase III randomized, controlled study, in patients with cirrhosis, ascites and HRS-1 [13], as defined by the ICA [14], compared the effects of terlipressin plus albumin versus placebo plus albumin on renal function. The REVERSE trial was approved by the ethics committees of all participating centres. The study design, protocol [10] and results have been described previously [13]. Briefly, patients with HRS-1 who did not have uncontrolled infection were included after obtaining informed consent and randomized to terlipressin or placebo, together with albumin [10, 13]. At enrollment, renal dysfunction severity was categorized into AKI stages based on ICA diagnostic criteria (Table 1) [3]. Because these patients were closely observed as either inpatients or outpatients before study enrollment, serial SCr readings were available during the pre-enrollment assessment period in most patients to calculate the change in SCr within 48 h [3]. If pre-enrollment SCr readings were not available, then a stable SCr within the previous 3 months was used as a baseline to calculate the change in SCr [3]. When neither a recent (≤48 h) nor a stable baseline SCr level within 3 months was available, the SCr taken at hospital admission was used as the baseline value to calculate the change in SCr and determine the AKI stage [3]. The ICA decided not to include the urine output criteria for the diagnosis of AKI in cirrhosis, as cirrhotic patients with ascites typically have small urine volume of ∼500 mL/day, even in the absence of a creatinine increase, due to their intense renal sodium and water retention [3]. Therefore urine output was not documented in these patients.

Terlipressin or placebo 1 mg was given every 6 h via slow intravenous bolus injections and albumin was dosed at 20–50 g/day [13]. Doses for terlipressin plus albumin or placebo plus albumin were increased to 2 mg every 6 h after a minimum of 10 doses if SCr had not decreased by at least 30% from the value at the beginning of treatment [13]. Treatment was allowed for up to 14 days or a maximum of 15 or 16 days if SCr reached 133 μmol/L (1.5 mg/dL) for the first time on Day 13 or 14, respectively. The primary study endpoint was confirmed HRS-1 reversal, defined as two SCr readings of ≤133 μmol/L (≤1.5 mg/dL) at least 48 h apart during treatment [13].

AKI stage progression or regression was assessed by evaluating the change in SCr from the start to end of treatment (EOT) [3]. AKI stage progression was defined as advancement to the next higher stage or initiation of renal replacement therapy (RRT) [3]. AKI stage regression was defined as a reduction of SCr to reach a lower stage [3]. The relationship between (i) the change in AKI staging from enrollment to EOT and (ii) confirmed HRS-1 reversal and 90-day patient survival was evaluated.

Statistical analysis

All continuous results are expressed as mean [standard deviation (SD)] and comparisons were made with analysis of variance [13]. All frequency variable results are presented as the number and percentage of patients and comparisons were made with a chi-square test. All analyses were based on the intent-to-treat population, defined as all randomized patients who had at least one baseline assessment. Data from both the terlipressin and placebo arms were pooled to provide sufficient numbers for a meaningful analysis. Transplant-free survival and overall survival were defined as the percentage of patients alive at 90 days. Univariate logistic regression was used to evaluate baseline characteristics on AKI improvement from baseline to the EOT. The Cochran–Armitage trend test was used to evaluate a trend across a reduction in AKI stage, no change in AKI stage and an increase in AKI stage for adverse events (AEs). The change in AKI stage, with the percentage of patients alive at 90 days, was assessed using linear regression analysis. A P-value <0.05 was considered statistically significant.

All authors had access to study data and have reviewed and approved the final manuscript.

RESULTS

In all, 184 of 196 patients who were enrolled into the REVERSE trial [13] had data available to calculate the change in SCr, enabling AKI diagnosis and staging, were included in this analysis. AKI stages were diagnosed using the SCr changes only. Baseline patient demographic and clinical characteristics are presented in Table 2. These middle-aged, predominantly male patients had alcohol as the most common etiology of cirrhosis. The majority of patients had advanced liver disease as suggested by their Child–Pugh Class C status [15] and high Model for End-Stage Liver Disease (MELD) scores. Bacterial infection in the previous 14 days was common; urinary tract infection and spontaneous bacterial peritonitis were the most common infections. A total of 91 patients received terlipressin and 93 received placebo.

Table 2. Baseline patient demographics and laboratory data

Variable	AKI Stage 1 ($n = 51$)	AKI Stage 2 ($n = 68$)	AKI Stage 3 ($n = 65$)	P-value
Age (years), mean (SD)	57.3 (7.0)	55.7 (8.8)	54.2 (8.8)	0.1362
Sex (male:female), *n*	29:22	41:27	42:23	0.6921
Alcoholic hepatitis, *n* (%)	13 (25.5)	14 (20.6)	16 (24.6)	0.7874
Aetiology of cirrhosis,[a] *n* (%)				
Alcohol	29 (56.9)	35 (51.5)	34 (52.3)	0.8282
Viral hepatitis	19 (37.3)	36 (52.9)	21 (32.3)	0.0426
Cholestatic	3 (5.9)	4 (5.9)	0 (0.0)	0.1371
Cryptogenic	4 (7.8)	2 (2.9)	7 (10.8)	0.2053
Other	4 (7.8)	12 (17.6)	11 (16.9)	0.2667
MAP (mmHg), mean (SD)	75 (11)	75 (10)	77 (13)	0.4244
Heart rate (beats/min), mean (SD)	82 (12)	78 (12)	80 (13)	0.2885
SCr at AKI diagnosis (μmol/L), mean (SD)	239 (28)	301 (31)	415 (89)	<0.0001
SCr at AKI diagnosis (mg/dL), mean (SD)	2.7 (0.32)	3.4 (0.35)	4.7 (1.01)	
Patients with SCr ≥318 μmol/L (≥3.6 mg/dL), *n* (%)	1 (2.0)	24 (35.3)	59 (90.8)	<0.0001
Δ SCr at end of treatment (μmol/L), mean (SD)	27 (103)	27 (124)	27 (185)	0.9829
Δ SCr at end of treatment (mg/dL), mean (SD)	−0.3 (1.17)	−0.3 (1.40)	−0.3 (2.09)	
Serum sodium (mmol/L), mean (SD)	132.4 (5.8)	132.2 (6.5)	132.5 (6.1)	0.9524
Serum bilirubin (μmol/L), mean (SD)	121 (132)	221 (233)	226 (192)	0.0081
Serum bilirubin (mg/dL), mean (SD)	7.1 (7.7)	12.9 (13.6)	13.2 (11.2)	
Serum albumin (g/L), mean (SD)	36.0 (7.0)	36.0 (7.0)	34.0 (7.0)	0.1907
Haemoglobin (g/L), mean (SD)	87.0 (17.0)	87.0 (14.0)	89.0 (14.0)	0.6249
WBC count ($\times 10^9$/L), mean (SD)	8.0 (5.9)	6.7 (3.6)	9.0 (5.2)	0.0281
INR (%), mean (SD)	2.2 (0.93)	2.3 (0.72)	2.3 (0.78)	0.8891
Child–Pugh score, mean (SD)	10.2 (1.77)	10.4 (1.81)	10.5 (1.71)	0.5653
Child–Pugh score class C, *n* (%)	34 (66.7)	41 (60.3)	45 (69.2)	0.5392
MELD score, mean (SD)	29.7 (5.65)	34.2 (5.06)	34.8 (5.47)	<0.0001
CLIF-SOFA score, mean (SD)	8.6 (2.1)	9.7 (1.9)	10.6 (2.1)	<0.0001
Prior infection in ≤14 days, *n* (%)				
Pneumonia	7 (13.7)	2 (2.9)	0 (0.0)	0.0020
Urinary tract infection	13 (25.5)	10 (14.7)	18 (27.7)	0.1608
Spontaneous bacterial peritonitis	13 (25.5	9 (13.2)	9 (13.8)	0.1518
Other	6 (11.8)	5 (7.4)	8 (12.3)	0.5949
Spot urine sodium (mEq/L), mean (SD)	11.8 (10.2)	17.4 (16.5)	22.3 (23.5)	0.0542

[a]Some patients had more than one aetiology for their cirrhosis.

CLIF-SOFA, Chronic Liver Failure–Sequential Organ Failure; INR, international normalized ratio; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; Rx, treatment ΔSCr, change in serum creatinine; SD, standard deviation WBC, white blood cell.

Renal function

All patients had stable and normal SCr before study entry. Despite this, SCr at AKI diagnosis varied widely, with approximately one-third of patients finally reaching each AKI stage (Table 2). The precipitant for reaching a final higher AKI stage is unclear, although patients in AKI Stage 3 had a significantly higher baseline serum bilirubin level and higher baseline Chronic Liver Failure–Sequential Organ Failure score, suggesting more severe liver dysfunction [16]. Similar numbers of patients receiving terlipressin versus placebo were at various AKI stages at diagnosis (Stage 1: 25 versus 26; Stage 2: 37 versus 35; Stage 3: 31 versus 34; $P = 0.91$). SCr levels at the time of AKI diagnosis were similar between the two treatment groups (Supplementary data, Table S1). Although SCr reduction from AKI diagnosis to EOT was similar for the three AKI stages, patients receiving terlipressin experienced a significantly higher mean reduction in SCr at EOT compared with those receiving placebo: −44 (SD 136) μmol/L versus −9 (SD 148) μmol/L ($P < 0.001$). With treatment, 89 (48%) patients had no change in AKI stage at EOT (Supplementary data, Table S2). In all, 34 of 91 (37%) patients receiving terlipressin had a decrease in AKI stage at EOT versus 25 of the 93 (27%) patients receiving placebo, while the AKI stage increased by EOT in 13 of 91 (14%) patients receiving terlipressin versus 23 of 93 (25%) patients receiving placebo (Supplementary data, Table S2). Neither comparison was statistically significant. Concentrating on the 148 patients who had no AKI stage progression (i.e. unchanged or reduced AKI stage at EOT), AKI stage regression was most commonly observed in patients with an initial AKI Stage 2, with 28 of 47 (60%) patients achieving a reduction in AKI stage by EOT (Figure 1). In all, 17 of 34 (50%) patients receiving terlipressin who had an AKI stage reduction had confirmed HRS reversal. This compared with 9 of 25 (36%) patients receiving placebo ($P = 0.30$).

RRT was started in 55 of 148 (37%) patients who showed no progression in AKI for a variety of reasons, including volume overload, acidosis, electrolyte abnormalities, worsening renal failure and preparation for liver transplantation. More patients with an initial Stage 3 AKI required RRT [34/65 (52%)]. Significantly fewer patients who had a decrease in AKI stage required RRT [9/59 (15%)] compared with patients who had no change in AKI stage with treatment [46/89 (52%)]. This was especially true in patients whose initial AKI was at Stage 3 ($P < 0.0001$) (Figure 1A).

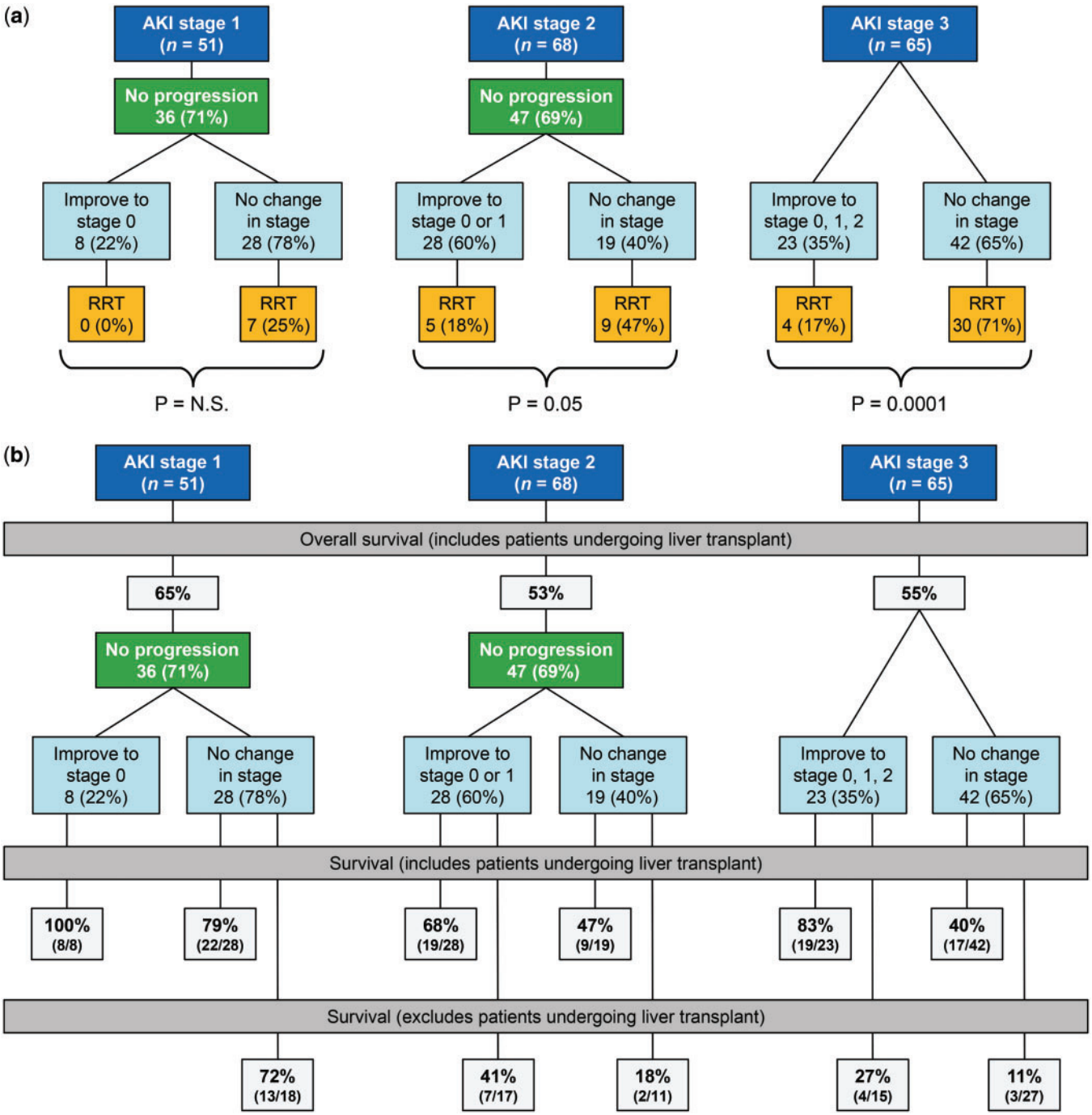

FIGURE 1: Incidence and extent of AKI improvement and (**a**) the need for RRT and (**b**) subsequent 90-day survival. AKI, acute kidney injury; RRT, renal replacement therapy.

Other clinical outcomes

A total of 175 of 184 (95%) patients experienced AEs during the study. Of these, 109 (62%) were serious AEs (SAEs). The most common SAEs were hepatic encephalopathy, infection of any kind and gastrointestinal bleeding. Table 3 shows the breakdown of AEs and SAEs according to whether patients had a reduction, no change or progression of AKI stage with treatment. Patients with AKI stage progression despite treatment had significantly more episodes of SAEs, especially significantly more episodes of hepatic encephalopathy. No significant difference in the occurrence of gastrointestinal bleeding or infections was observed among patients with the various courses of AKI.

Predictors of decrease in AKI stage with treatment

Various parameters were evaluated for the ability to predict a reduction in AKI stage with treatment (Table 4). The parameters with significance <0.10 were then fitted into a multivariate analysis model to determine the factors that were capable of predicting

Table 3. List of AEs reported in patients in the various categories of AKI

AEs	Reduction in AKI stage ($n = 59$)	No change in AKI stage ($n = 89$)	Increase in AKI stage ($n = 36$)	Three-variable chi-square P-value	Two-variable chi-square P-value	Cochran–Armitage trend P-value
Any AE	54 (91.5)	87 (97.8)	34 (94.4)	0.2231	0.8368	0.3651
Any SAE	26 (44.1)	56 (62.9)	27 (75.0)	0.0073	0.0319	0.0019
Hepatic encephalopathy	11 (18.6)	15 (16.9)	12 (33.3)	0.1074	0.0361	0.1389
GI bleed	4 (6.8)	4 (4.5)	3 (8.3)	0.6800	0.5063	0.8691
Infection	8 (13.6)	25 (28.1)	11 (30.6)	0.0742	0.2975	0.0379

Values presented as *n* (%). AE, adverse event; GI, gastrointestinal; SAE, severe adverse event.

Table 4. Univariate logistic regression of baseline characteristics on improvement in AKI from baseline to end of treatment

Baseline parameter	*n*	Relative risk (95% CI)	P-value
Age <65 years	184	1.4667 (0.6586–3.2664)	0.3485
Alcoholic hepatitis not present	184	0.6420 (0.4192–0.9832)	0.0416
MAP	184	1.0094 (0.9907–1.0285)	0.3245
MAP<70 mmHg	184	0.9817 (0.6254–1.5408)	0.9359
MELD score	162	0.9861 (0.9483–1.0253)	0.4814
SCr	184	0.9397 (0.7720–1.1437)	0.5347
SCr as a categorical variable			
221–265 versus <221 μmol/L (2.5–3.0 versus <2.5 mg/dL)	184	0.3000 (0.1099–0.8189)	0.0003
>265–442 versus <221 μmol/L (>3–5 versus <2.5 mg/dL)	184	1.0455 (0.5165–2.1166)	
>442 versus <221 μmol/L (>5 versus <2.5 mg/dL)	184	0.4174 (0.1370–1.2719)	
Total bilirubin	177	0.9829 (0.9609–1.0053)	0.1338
Male gender	184	1.5882 (0.9834–2.5650)	0.0585
Precipitating factors for HRS-1	184	1.0372 (0.6806–1.5807)	0.8650
Prior rifaximin	184	0.8963 (0.5840–1.3757)	0.6166
Terlipressin treatment group	184	1.3899 (0.9060–2.1322)	0.1316
Baseline urine sodium	116	1.0027 (0.9922–1.0135)	0.6125

CI, confidence interval; HRS-1, type 1 hepatorenal syndrome MAP, mean arterial pressure; MELD, Model for End-stage Liver Disease; SCr, serum creatinine.

a reduction in AKI stage. Only an absence of alcoholic hepatitis was a predictor for a reduction in AKI stage with treatment.

Survival

The overall survival, including patients who underwent liver transplantation, was not significantly different based on AKI stage, varying between 53% and 65%. For the 148 patients who showed no AKI progression, the overall 90-day survival was consistently better in the patients who showed a decrease in AKI stage with treatment without the need for RRT when compared with those who had no change in AKI stage with treatment, no matter what the initial AKI stage was and regardless of whether patients underwent liver transplantation (Figure 1B). Patients who seemed to derive the most benefits from down-staging of AKI were those who were in AKI Stage 1 at initial diagnosis. For the patients who did not show down-staging of AKI and who also required RRT, 90-day survival was inversely proportional to the initial stage of AKI (Figure 1B). A strong association was found between the change in AKI stage with treatment and overall 90-day survival (r^2 =0.9242, P = 0.0022) (Figure 2). A decrease in one stage of AKI with treatment was associated with an estimated additional 18% improvement in overall 90-day survival based on the correlation slope shown in Figure 2. AKI progression by one stage higher was associated with a similar estimated reduction in overall 90-day survival (Figure 2).

DISCUSSION

HRS-1 in cirrhosis is associated with a poor prognosis if left untreated [4]. Although therapies aim to correct the underlying pathophysiology of the abnormal haemodynamics of systemic vasodilatation and renal vasoconstriction, improvement in survival has been negligible [8, 13, 17, 18]. Even with meta-analyses that have assessed the beneficial effects of systemic/splanchnic vasoconstrictors in patients with HRS-1, improvement in short-term survival was only moderate [11, 12], especially when low-quality studies were excluded. This is somewhat surprising, especially when the vasoconstrictor studies were designed to reverse the pathophysiology of HRS-1. However, this may be related to the fact that survival following treatment is linked to HRS reversal, which is defined as SCr reduction to <133 μmol/L (<1.5 mg/dL) [14]. This may be easily achievable if the peak SCr reached is slightly over the diagnostic SCr threshold for HRS-1 of 226 μmol/L (2.5 mg/dL) [14]. However, if the peak SCr reached is significantly higher than the diagnostic threshold, it is much more difficult to achieve HRS reversal [14]. Indeed, a peak SCr >619 μmol/L (>7.0 mg/dL) was shown to be a predictor of non-response to systemic/splanchnic vasoconstrictor treatment [19]. The next obvious question is whether survival following the development of HRS-1 is contingent upon HRS reversal. This does not appear to be the case, as we have previously shown that survival in

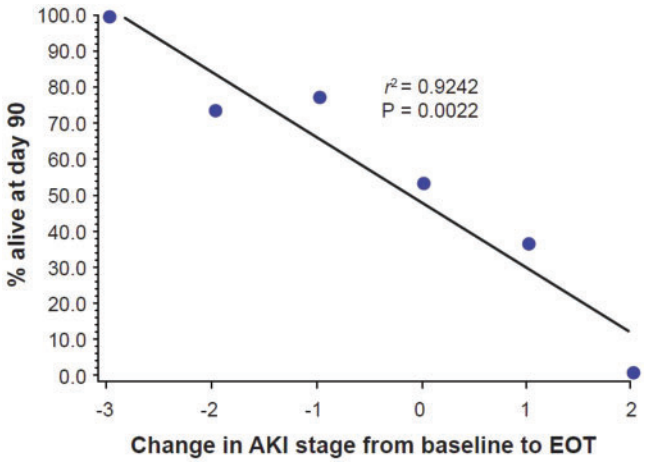

FIGURE 2: Correlation between change in AKI stage and survival. AKI, acute kidney injury; EOT, end of treatment.

patients with HRS-1 receiving terlipressin correlated significantly with the percent change in SCr [20] (i.e. the greater the decrease in SCr, the better the survival of the patients). Even a small reduction of >20% in SCr was sufficient to confer improvement in 90-day survival despite the absence of HRS reversal [20]. Therefore, assessment of survival following systemic/splanchnic vasoconstrictor treatment should be based on the extent of renal function improvement rather than the renal function reaching a rigid threshold. A recent meta-analysis of seven clinical studies consisting of 345 patients with HRS-1 confirmed a significant correlation between the change in creatinine with vasoconstrictor treatment and the reduction in relative risk for mortality [21]. In patients surviving the treatment period, a decrease in creatinine of 88 µmol/L (1 mg/dL) while on treatment resulted in a 16% reduction in relative risk for post-treatment mortality during follow-up [21].

With the revised definition of renal dysfunction in cirrhosis and introduction of the AKI staging concept [3], the severity of HRS-1 in cirrhosis can now be described as different AKI stages depending on the peak SCr reached relative to the baseline SCr. Renal function improvement with HRS-1 treatment can also be expressed as a reduction in AKI stage. Thus, in patients with HRS-1 whose renal dysfunction did not progress with treatment, a reduction in AKI stage without necessarily achieving HRS reversal was associated with improved survival, especially compared with patients who showed no change in AKI stage with treatment [3]. This once again confirms that the benefit of HRS-1 treatment can be evaluated by renal function improvement rather than complete HRS reversal. In fact, a reduction of AKI by one stage is associated with an 18% improvement in the percentage of patients alive at 90 days. This has potentially significant implications in managing cirrhotic patients with HRS-1. Traditionally, successful treatment of HRS-1 was defined by HRS reversal. Patients without HRS reversal receiving pharmacotherapy were usually given priority for liver transplantation, which was regarded as the definitive treatment for HRS-1, with a much more robust HRS reversal rate approaching 75% [22]. This new knowledge means cirrhotic patients with HRS-1 who experience AKI stage reduction with pharmacotherapy could potentially wait for their liver transplant, while those with AKI stage progression could be given priority for liver transplantation. Of course, this is only speculative, as this study did not specifically set out to determine the relationship between AKI stage reduction and wait time for liver transplantation. This is an area of much controversy as many believe that even patients with HRS reversal do not necessarily have protection against a reduction in glomerular filtration rate following liver transplantation [23], despite a reduction in pre-transplant MELD score [24], and therefore should maintain their priority for liver transplantation [25].

It should be noted that patients who experienced a reduction in AKI stage also had the fewest SAEs and the lowest incidence of complications, such as hepatic encephalopathy and bacterial infections, compared with patients who showed no change or progression of AKI stage with treatment. Infections are known to induce a cytokine storm and cause an intense inflammatory response, sometimes overwhelming the host's immunological defense system [26]. Furthermore, various molecules derived from the pathogens known as pathogen-associated molecular patterns can cause a further reduction in the already sluggish flow within the renal microcirculation, thereby preventing improvement in renal blood flow and renal function [26].

Although AKI stage reduction with treatment was associated with improved survival in patients with Stage 3 AKI at the time of HRS-1 diagnosis, improvement was certainly less when compared with patients with lower stages of AKI at HRS-1 diagnosis. Patients with AKI who had the greatest change SCr were more likely to have a progressive AKI course, which was associated with significantly reduced 30-day survival [27]. In fact, a large change in SCr during an AKI episode has been the strongest factor impacting AKI outcomes and survival [27, 28]. The corollary from this observation is that HRS-1 treatment should begin as soon as the diagnostic criteria are met, which means as soon as there is doubling of SCr without regard for a particular SCr threshold to be reached [3]. Otherwise, the possibility of a reduction in AKI stage and the likelihood for survival are significantly reduced.

Despite the baseline SCr being an important parameter in the management of patients with HRS-1, it was not a significant predictor of AKI stage reduction with treatment, whether expressed as a continuous variable or as a categorical variable. Rather, the only factor that could predict AKI stage reduction with treatment was the absence of alcoholic hepatitis. Alcoholic hepatitis is an inflammatory condition [29, 30]. The systemic inflammatory syndrome has been shown to occur in approximately half of patients with alcoholic hepatitis, irrespective of the presence of a bacterial infection [29, 30]. The presence of systemic inflammatory syndrome, in turn, is associated with the development of multi-organ failure, with renal failure being the most common organ failure following liver failure, occurring in at least one-third of patients [29]. Cirrhosis is associated with various markers of inflammation, such as increased white blood cell count and C-reactive protein, as well as the presence of various inflammatory cytokines and oxidative stress [31, 32]. The presence of alcoholic hepatitis has been associated with further

exaggeration of the inflammatory process, as alcohol has a damaging effect on the integrity of the gut mucosal barrier, favouring an increase in bacterial translocation [29]. Indeed, increased levels of lipopolysaccharide have been reported in patients with alcoholic cirrhosis without overt infection [29]. Alcohol itself is a hepatotoxin and its metabolism leads to the production of reactive oxygen species, inducing hepatocyte apoptosis. Therefore, in patients with alcoholic hepatitis, there is an overabundance of pathogen-associated molecular patterns from the increased bacterial translocation, as well as molecules known as damage-associated molecular patterns derived from direct alcohol damage to hepatocytes [29]. The fact that an anti-inflammatory agent such as pentoxifylline can prevent the development of HRS-1 in patients with alcoholic hepatitis supports this contention [33]. Therefore, in patients with alcoholic hepatitis, clinicians need to be vigilant for the development of AKI, especially in patients who have some degree of renal dysfunction at baseline.

This study has the limitation of not including the urine output in the AKI staging diagnosis, which may have reclassified the staging of these patients. At the time the REVERSE study was conceived, the concept of AKI in cirrhosis was only just germinating, hence only patients who fulfilled the classic diagnostic criteria of HRS-1 were included in the original study and collecting urine output data were not mandatory for the REVERSE study. A recent study suggested that including the urine output data in calculating the AKI stages may actually show a greater negative impact of higher AKI stage in cirrhosis [34] and therefore, by deduction, the reduction of stages using such a staging system may actually show greater benefits.

In summary, this study has shown that a reduction in AKI stage using SCr diagnostic criteria only following treatment of HRS-1 in cirrhosis is an important milestone in the management of these patients. HRS-1 reversal may be an unattainable goal for many patients, especially for patients whose peak SCr is several-fold higher than baseline. Recognizing that a reduction in AKI stage improves survival may allow a more realistic discussion about prognosis. The absence of alcoholic hepatitis is likely to allow a reduction in AKI stage with treatment. Treatment should begin when HRS-1 is diagnosed, as a higher AKI stage at diagnosis will reduce the prospect of AKI stage reduction and negatively impact the patient's prognosis.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

F.W., T.D.B., A.J.S. and S.C.P. conceived and designed the study. F.W., T.D.B., A.J.S., S.C.P., S.E. and KJ. contributed to the generation, collection, assembly, analysis and/or interpretation of data. F.W., T.D.B., A.J.S., S.C.P., S.E. and K.J. drafted and/or revised the manuscript. F.W., A.J.S., S.C.P., S.E. and K.J. were involved in the approval of the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

F.W. served as a consultant for Mallinckrodt Pharmaceuticals and received grant/research support from Grifols. T.D.B. served as a consultant for Mallinckrodt Pharmaceuticals and received grant/research support from AbbVie, Gilead and Merck. A.J.S. is president of Sanyal Biotechnology; has stock options in Exhalenz, Durect, Genfit, Indalo and Tiziana; served as a consultant for Abbott, Boehringer Ingelheim, Birdrock, Conatus, Eli Lilly, Ferring, Genentech, Gilead, Homoshear, Medimmune, Merck, Novartis, Novo Nordisk, Orphan Therapeutics, Pfizer, Salix, Sanofi, Surrozen and Tern; served as an unpaid consultant for Intercept, Prosciento; and received grant/research support from Bristol-Myers Squibb, Boehringer Ingelheim, Conatus, Gilead, Mallinckrodt Pharmaceuticals, Merck, Novartis and Salix. S.C.P. served as a consultant for Orphan Therapeutics. S.E. and K.J. are employees of Mallinckrodt Pharmaceuticals.

The results presented in this article have not been published previously in whole or part, except in abstract format.

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