Case Report

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Continuous recurrence of type 1 hepatorenal syndrome and long-term treatment with terlipressin and albumin: A new exception to MELD score in the allocation system to liver transplantation?

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Background & Aims: The recurrence of type 1 hepatorenal syndrome has been described in up to 20% of responders to terlipressin and albumin after the discontinuation of the treatment. Subsequent recurrence of type 1 hepatorenal syndrome may require long-term treatment with terlipressin and albumin.

Methods: We describe our experience of long-term administration of terlipressin as a bridge to LT in three patients with cirrhosis and recurrent type 1 hepatorenal syndrome. For all three patients we requested an "early transplant" which is an option recognized in our country to reduce waiting times for liver transplantation.

Results: All three patients were transplanted within 2 months of onset of hepatorenal syndrome. All patients are still alive and none of them have developed chronic kidney disease.

Conclusions: The outcomes of these patients suggest that long-term treatment with terlipressin and albumin is effective and well tolerated in patients with continuous recurrence of type 1 hepatorenal syndrome and, therefore, should be considered an absolute priority criterion in the allocation system for liver transplantation.

Introduction

Type 1 hepatorenal syndrome (HRS) is a phenotype of acute renal failure that often occurs in patients with cirrhosis and ascites. Type 1 HRS develops as a result of a severe reduction of effective circulating volume due to both an extreme splanchnic arterial vasodilatation and a reduction of cardiac output [1]. The optimal and definitive treatment of type 1 HRS is liver transplantation (LT). Nevertheless, the prognosis of type 1 HRS is so poor that it can reduce the probability of undergoing LT. The administration of terlipressin and albumin has been shown to be effective in the treatment of type 1 HRS since it can restore renal function in 35–46% of cases. Additionally, a good response to this treatment is associated with an improvement in survival rates and outcome of LT. A complete response to terlipressin and albumin has been defined as a reduction of serum creatinine below 1.5 mg/dl (133 μmol/L) [1]. The length of treatment should be extended for a maximum of 14 days in patients with partial or no response [1]. After the withdrawal of treatment type 1 HRS can recur in up to 20% of the cases [2]. It has been stated that the recurrence of type 1 HRS can be reverted with a re-treatment with terlipressin and albumin [1]. This therapeutic strategy can result in a long-term administration of terlipressin and albumin until the time of LT in patients with continuous recurrence of type 1 HRS [3]. Taking into account that neither continuous recurrence of type 1 HRS nor long-term treatment of type 1 HRS is now considered to be an exception to Model of End-stage Liver Disease (MELD) score in the organ allocation system, this policy can negatively affect the outcome after LT [3]. Here we described three patients with cirrhosis, ascites and continuous recurrence of type 1 HRS who underwent long-term treatment with terlipressin and albumin before successfully undergoing LT.

Case report

Case 1

In November 2009 a 61-year-old man affected by alcohol-related cirrhosis (abstinent from 2007), who was regularly followed as an outpatient by our Unit for refractory ascites, was admitted to our Liver Unit for spontaneous bacterial peritonitis (SBP) and acute renal failure (serum creatinine 446 μmol/L; 5.04 mg/dl). On

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Abbreviations: HRS, hepatorenal syndrome; LT, liver transplantation; MELD, Model of End Stage Liver Disease; ICA, International Club of Ascites; NIT, North Italian Transplant; UTI, urinary trait infection; SBP, spontaneous bacterial peritonitis; CNIs, calcineurin inhibitors.

admission, antibiotic therapy was promptly started with a resolution of SBP. One week before hospitalization serum creatinine was only lightly increased (128 μmol/L; 1.45 mg/dl), and a diagnosis of type 1 HRS was made according to the International Club of Ascites (ICA) criteria [2], leading to the administration of terlipressin by continuous intravenous infusion and i.v. albumin [2]. At the same time, the ongoing administration of propanolol was discontinued. After the normalization of renal function on day 15, the treatment was discontinued. Within the following 48 h serum creatinine increased up to 218 μmol/L (2.47 mg/dl) (Fig. 1), so treatment with terlipressin and albumin was reintroduced. A urinary trait infection (UTI) on day 23 further complicated the clinical course of the disease during the following days causing renewed deterioration of renal function, which was reverted by increasing the daily dose of terlipressin up to 6 mg. On day 33 the treatment was discontinued after a slow tapering of the dose of terlipressin. On day 35, in the absence of a precipitating factor, a new episode of type 1 HRS occurred leading to the reactivation of treatment with terlipressin and albumin, and a request for "early" LT was submitted first to the local Committee for LT and then to the organ procurement agency of our area, the North Italian Transplant (NIT). A request for an "early transplant" within the NIT can be advanced for an hospitalized candidate to LT with a MELD score >25. When a request for an "early transplant" is presented to the NIT, the transplant center which would receive the graft on a regular basis can opt to give it to the center which requests an "early transplant", as part of a gentlemanly agreement. At the time of our request the MELD score and the MELD-Na score, which were calculated based on the value of serum creatinine on day 35 were 19 ("actual" MELD score) and 19 ("actual" MELD-Na score). Nevertheless, our request was sustained by the fact that the need for continuous and long-term treatment with terlipressin and albumin was recognized and accepted as an exception to MELD by NIT. Our request was accepted on the basis of a simple evaluation: if the MELD score was calculated by reviving the peak value of creatinine during the last episode of type 1 HRS the "real" MELD score and the "real" MELD-Na score of the patient would have been 30 and 34, respectively. On day 55, while still being treated with terlipressin at the daily dose of 6 mg, and albumin, the patient underwent LT (Fig. 1). The "actual" as well as the "real" MELD and MELD-Na scores at the time of LT are reported in Fig. 2. After LT, in order to reduce the calcineurin inhibitors (CNIs) -induced nephrotoxicity, a low dose of tacrolimus (target trough tacrolimus level <5 ng/ml) was used together with mycophenolate mofetil. Eleven months after LT the patient is in good clinical condition with normal renal function (Fig. 3).

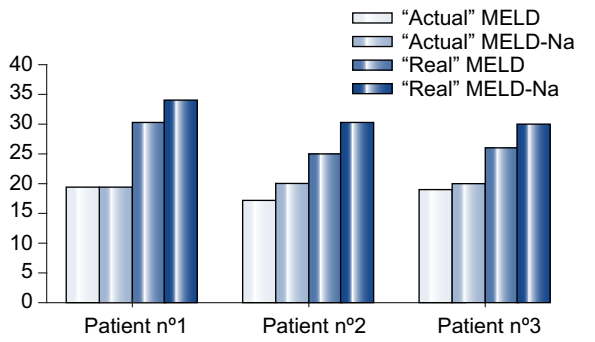

Fig. 2. Model of End Stage Liver Disease (MELD) score, Na-MELD. 'Actual' values were calculated on the basis of the serum creatinine value during treatment. 'Real' values were calculated on the basis of the peak value of serum creatinine during the last episode of type 1 HRS.

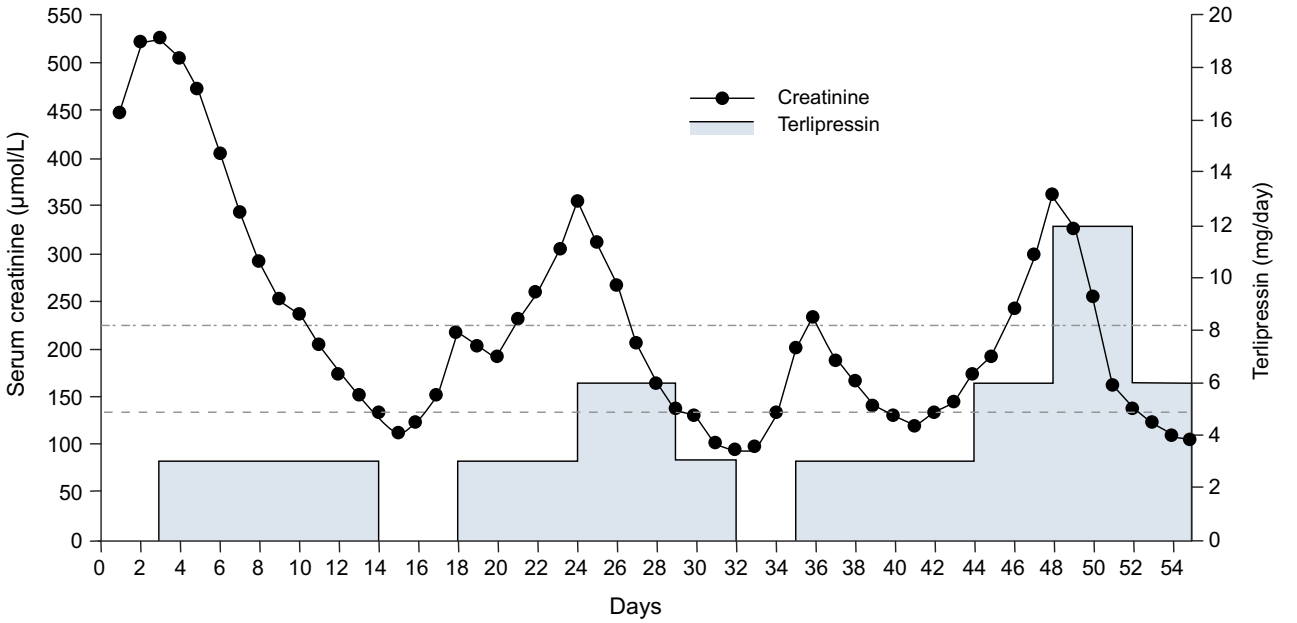

Fig. 1. Time course of serum creatinine and treatment with terlipressin and albumin in patient 1. The daily dose of terlipressin is also indicated. Albumin was administered at the dose of 20–40 g/day for the duration of treatment with terlipressin. Dotted line indicates a 133 μmol/L value of serum creatinine. Dashed line indicates a 226 μmol/l value of serum creatinine.

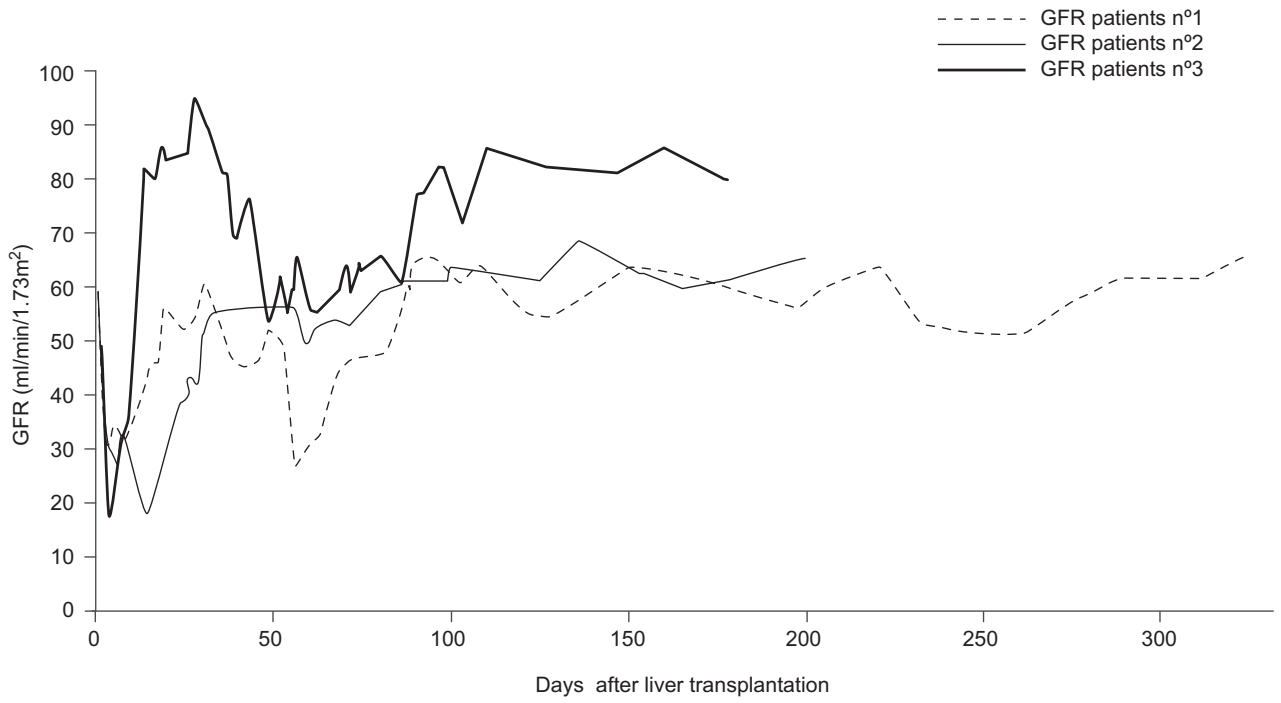

Fig. 3. Time course of glomerular filtration rate calculated on the basis of the Modification of Diet in Renal Disease (MDRD) equation after LT in the three patients.

Case 2

In February 2010 a 52-year-old man with a history of alcohol-related cirrhosis (abstinent from 2009) was admitted to our Liver Unit for refractory ascites and hepatic encephalopathy. On admission the patient presented ascites, severe hyponatremia (112 mmol/L) and renal impairment (serum creatinine 236 μmol/L; 2.67 mg/dl). Since the laboratory examinations carried out ten days before hospital admission showed that he had a normal renal function (serum creatinine 87 μmol/L; 0.98 mg/dl), a diagnosis of type 1 HRS was made according to ICA diagnostic criteria [2]. At this point terlipressin was administered as intravenous boluses at the daily dose of 3 mg associated with 20–40 g/day of albumin [2]. Renal function improved and after 10 days terlipressin and albumin were discontinued. During the following 72 h renal function progressively worsened, even without there being evidence of a precipitating factor. Therefore, treatment with terlipressin and albumin was restarted, producing a completely new response within five days. However, after the withdrawal of terlipressin and albumin a new recurrence of type 1 HRS occurred, making it necessary to restart the treatment. During the following twenty days, the patient maintained a good renal function and a normal serum sodium level even if an increase of the daily dose of terlipressin up to 4 mg was required to control another increase in serum creatinine. Another attempt at discontinuing treatment, even in a step-wise fashion, was soon followed by a further impairment of renal function, so on day 44 after admission the patient was still on treatment with terlipressin and albumin (Fig. 4). No terlipressin-related side effect was observed. On day 45, a request of "early" LT was advanced. On day 46 the patient underwent LT. The "actual" MELD score, the "actual" MELD-Na score as well as the "real" scores at the time of LT are reported on Fig. 2. After LT, in order to counteract CNIs-induced nephrotoxicity, mycophenolate mofetil and reduced dose tacrolimus were administered. Seven months after LT the patient is in good clinical condition and his renal function is normal (Fig. 3).

Case 3

In May 2010 a 46-year-old man with HCV and alcohol-related cirrhosis (abstinent from 2009) was admitted to our Liver Unit for refractory ascites and urinary trait infection (UTI). On admission serum creatinine was normal (97 μmol/L; 1.10 mg/dl). UTI was successfully treated with antibiotic therapy. After ten days the patient developed cellulitis and his renal function rapidly worsened (serum creatinine 225 μmol/L; 2.55 mg/dl). The diagnosis of type 1 HRS was made according to ICA criteria. Treatment with i.v. terlipressin and albumin was started together with antibiotic therapy with a complete response in 9 days. At the same time the ongoing treatment with propanolol was discontinued. On day 19 after admission terlipressin and albumin were discontinued. Within the following 48 h renal function worsened, despite the resolution of the infection, and terlipressin and albumin were restarted. A further attempt to withdraw the treatment at 27 day failed. Consequently, the treatment was started again and a request for "early transplant" was submitted. Treatment with telipressin and albumin was no longer discontinued. The daily dose of terlipressin was transiently doubled to cope with another increase in the serum creatinine level. Therefore, after 44 days from the onset of the first episode of type 1 HRS, while still under treatment (Fig. 5), the patient was transplanted. The "actual" as well as the "real" MELD and MELD-Na scores at the time of LT are reported on Fig. 2. Mycophenolate mofetil and

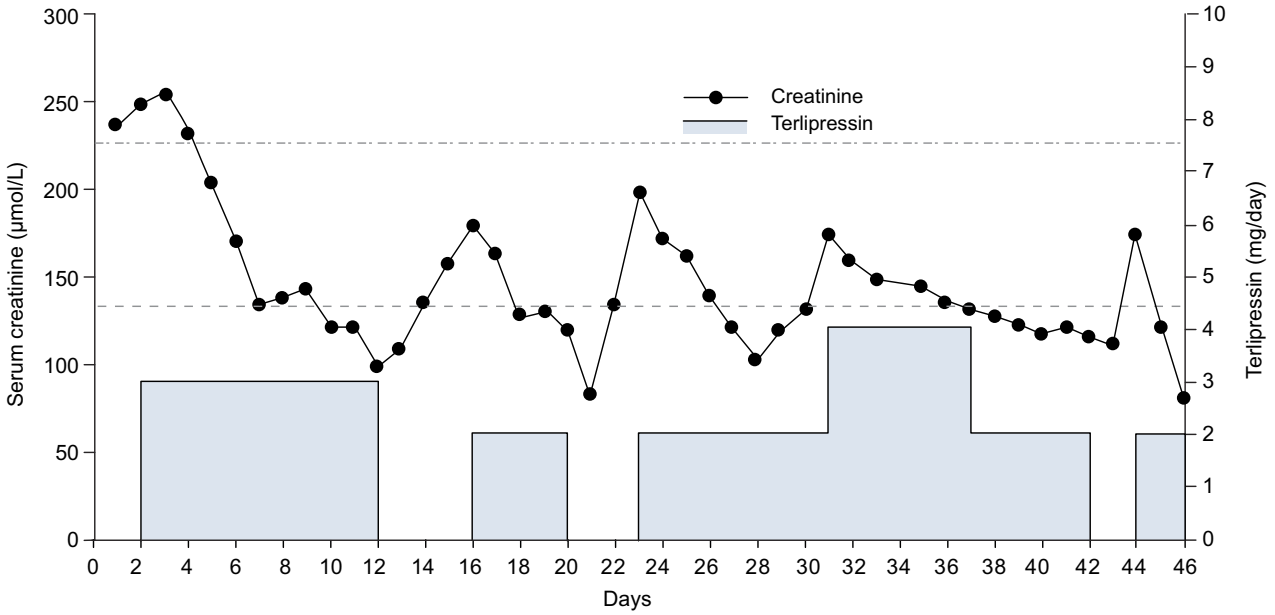

Fig. 4. Time course of serum creatinine and treatment with terlipressin and albumin in patient 2. The daily dose of terlipressin is also indicated. Albumin was administered at the dose of 20–40 g/day for the duration of treatment with terlipressin. Dotted line indicates a 133 μmol/L value of serum creatinine. Dashed line indicates a 226 μmol/L value of serum creatinine.

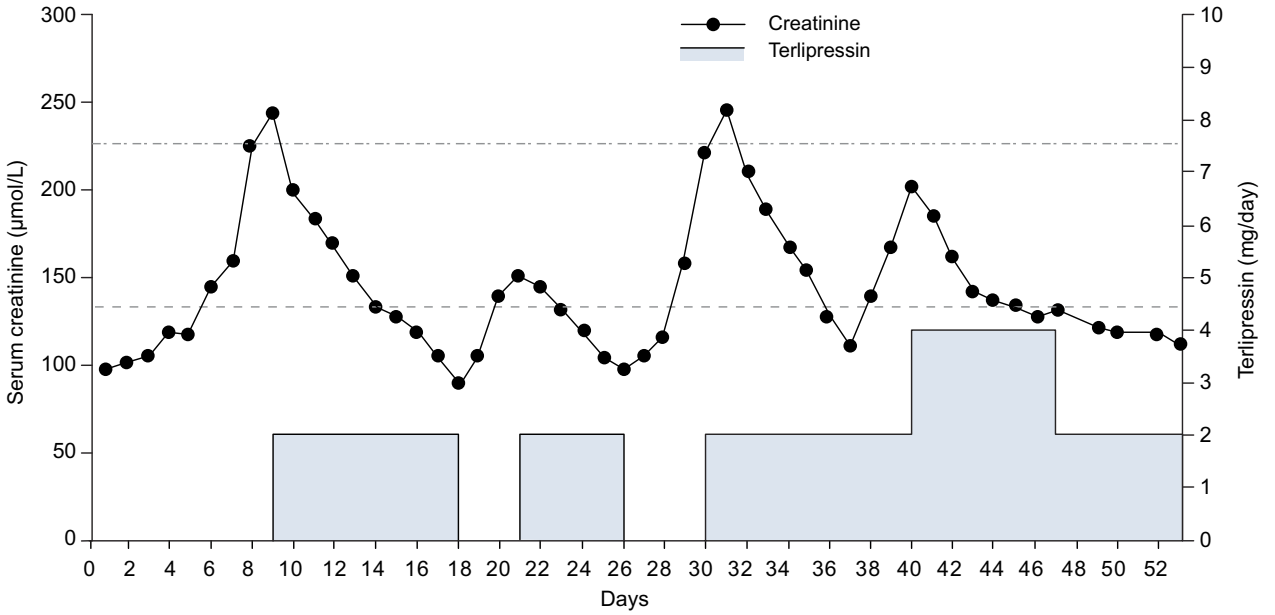

Fig. 5. Time course of serum creatinine and treatment with terlipressin and albumin in patient 3. The dose of terlipressin is also indicated. Albumin was administered at the dose of 20–40 g/day for the duration of treatment with terlipressin. Dotted line indicates a 133 μmol/L value of serum creatinine. Dashed line indicates a 226 μmol/L value of serum creatinine.

reduced dose cyclosporine were used as immunosuppressive strategy after LT. Six months after LT he is in good clinical condition with a normal renal function (Fig. 3).

Discussion

Type 1 HRS is a severe complication of cirrhosis with a highly negative impact on prognosis. It has been shown that terlipressin plus albumin is an effective treatment for type 1 HRS and that a good response to this treatment is associated with an improvement of both transplant-free survival and outcome of LT [4]. It is said that the mean time of treatment in responders is about 10–12 days and that a treatment longer than 14 days is not justifiable in case of no response or partial response [2]. Nevertheless, type 1 HRS can recur in up to 20% of patients, so that re-treatment with terlipressin and albumin is recommended in these patients [1]. Despite the efficacy of the treatment with terlipressin and albumin in patients with type 1 HRS, there are concerns about its impact on the timing of LT. Since 2002, MELD score has determined the priority in liver allocation in many countries. The existence of an exception to MELD was recognized in the initial development of the MELD-based liver allocation policy [5]. Type 1 HRS is not specifically considered to be among the exceptions to the MELD-based allocation system, even though it has been clearly demonstrated that patients with HRS have a worse outcome for any given MELD score than other patients with cirrhosis [6,7]. In addition, paradoxically, the response to treatment with terlipressin and albumin, reduces the MELD score and negatively affects the position of patients in the waiting list [3]. This problem cannot be solved considering the MELD Na score, since hyponatremia, which is frequent in patients with type 1 HRS, has been shown to be improved by the treatment with vasoconstrictors and albumin [8]. The extreme situation in this paradox is represented by patients with continuous recurrence of type 1 HRS who need a long-term treatment with terlipressin and albumin. To date, the prognostic impact of continuous recurrence of type 1 HRS has never been evaluated. Nevertheless, it is not unreasonable to speculate that it is even worse than that related to a single episode of HRS.

Here we have described three cases involving the long term use of terlipressin and albumin as a bridge to LT, in which we considered the absolute dependence on treatment as an exception to the MELD. These three cases were observed among a cohort of 24 consecutive patients who were admitted for type 1 HRS in our Liver Unit or who developed it during hospitalization. These three patients also represent the 60% of those with recurrent type 1 HRS after the withdrawal of the treatment. For the purposes of this report, we define as continuous recurrence of type 1 HRS a relapse of type 1 HRS more than once within 72 h after the discontinuation of treatment. Since it has been stated that 14 days is the maximum time necessary to treat an episode of type 1 HRS in partial responders [2], we consider the administration of terlipressin and albumin for more than 30 days as "long term" treatment, because it covers more than two subsequent episodes of type 1 HRS. Three preliminary observations can be made based on our experience. The first is that continuous recurrence of type 1 HRS is not a rare event. The second is that the way to discontinue treatment with terlipressin and albumin does not seem to affect the recurrence of type 1 HRS. The third is that a long-term treatment with terlipressin and albumin is effective and well tolerated in treating the continuous recurrence of type 1 HRS.

To the best of our knowledge only eight patients who received long-term treatment with terlipressin and albumin have been reported [3,9,10]. Only 5 out of these eight patients underwent LT, and only three of them were still alive 6 months after LT. The remaining two patients died soon after LT from septic shock or massive bleeding. For these two patients, the poor outcome after LT was attributed by the Authors to the high MELD score at the time of LT [3]. Taking into account the waiting time before LT and the lack of a request for an "early" transplant, it can be observed that the response to therapy probably delayed the time of LT in these patients. In fact, they were transplanted only when they had reached a MELD score of 23 and 25, respectively, despite a good renal function after a "dramatic clinical course which was characterized by recurrent infections and bleeding complications" [3]. In order to support this concept, taking into account the value of serum creatinine before the last re-treatment with terlipressin and albumin, the "real" MELD score in these two patients would have been 31 and 33, respectively. Consequently, the two patients who died soon after LT had waited for the graft more than 2 months from the first episode of type 1 HRS with a "real" MELD score $\geqslant$ 30, which is known to be associated with an increased mortality after LT [11].

In our patients, the inability to discontinue terlipressin and albumin for continuous recurrence of HRS was used as a criterion for proposing these patients for an "early transplant", as previously described in Case 1. Using this procedure, all our patients were transplanted within 2 months after the development of the first type 1 HRS with an actual MELD within 17–19 and a "real" MELD within 25–30 respectively (Fig. 2). In keeping with the previous observation [4], the outcome of LT in our patients was excellent since (a) all them are alive at $\geqslant$6 months after LT, (b) none required renal replacement therapy after LT and (c) none of them developed chronic kidney disease [12] after LT. We realize that the request for an "early transplant" is an option limited to our country, which does occur in most other countries. We are also aware that the decision-making in such a critical situation cannot be entrusted simply to a gentlemen's agreement among different transplant centers. Therefore, while we wait for the acceptance by the transplant community of the use of prognostic formulae including not only MELD score and serum sodium, but also the occurrence of HRS [7], we propose that at least a long-term treatment of type 1 HRS with terlipressin and albumin for the continuous recurrence of this complication is considered as a priority criterion for organ allocation. This can be made either by considering the long term treatment of type 1 HRS as an exception to MELD or including it in the calculation of MELD score already provided for renal replacement therapy.

Conflict of interest

The authors who have taken part in this study declared that they do not have a relationship with the manufacturers of the drugs involved either in the past or present and they did not receive funding from the manufacturers to carry out their research.

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