Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Urinary neutrophil gelatinase-associated lipocalin predicts kidney outcome and death in patients with cirrhosis and bacterial infections

Rogelio Barreto[1,2,3,4,†], Chiara Elia[1,2,3,4,†], Elsa Solà[1,2,3,4], Rebeca Moreira[1,2,3,4], Xavier Ariza[1,2,3,4], Ezequiel Rodríguez[1,2,3,4], Isabel Graupera[1,2,3,4], Ignacio Alfaro[1,2,3,4], Manuel Morales-Ruiz[2,3,5], Estaban Poch[2,6], Mónica Guevara[1,2,3,4], Javier Fernández[1,2,3,4], Wladimiro Jiménez[2,3,5], Vicente Arroyo[1,2,3,4], Pere Ginès[1,2,3,4,*]

[1]*Liver Unit, Hospital Clínic, University of Barcelona, Barcelona, Catalunya, Spain;* [2]*Institut d'Investigacions Biomèdiques August-Pi-Sunyer (IDIBAPS), Spain;* [3]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHED), Spain;* [4]*Instituto Reina Sofía de Investigación Nefrológica (IRSIN), Spain;* [5]*Biochemistry and Molecular Genetics Department, University of Barcelona, Barcelona, Catalonia, Spain;* [6]*Hospital Clínic, Nephrology Unit, University of Barcelona, Barcelona, Catalonia, Spain*

Background & Aims: Infections in cirrhosis are frequently complicated by kidney dysfunction that entails a poor prognosis. Urinary biomarkers may be of potential clinical usefulness in this setting. We aimed at assessing the value of urinary neutrophil gelatinase-associated lipocalin (uNGAL), a biomarker overexpressed in kidney tubules during kidney injury, in predicting clinical outcomes in cirrhosis with infections.

Methods: One-hundred and thirty-two consecutive patients hospitalized with infections were evaluated prospectively. Acute kidney injury (AKI) was defined according to AKIN criteria. uNGAL was measured at infection diagnosis and at days 3 and 7 (ELISA, Bioporto, DK).

Results: Patients with AKI (n = 65) had significantly higher levels of uNGAL compared to patients without AKI (203 ± 390 *vs.* 79 ± 126 μg/g creatinine, p <0.001). Moreover, uNGAL levels were significantly higher in patients who developed persistent AKI (n = 40), compared to those with transient AKI (n = 25) (281 ± 477 *vs.* 85 ± 79 μg/g creatinine, p <0.001). Among patients with persistent AKI, uNGAL was able to discriminate type-1 HRS from other causes of AKI (59 ± 46 *vs.* 429 ± 572 μg/g creatinine, respectively; p <0.001). Moreover, the time course of uNGAL was markedly different between the two groups. Interestingly, baseline uNGAL levels also predicted the development of a second infection during hospitalization. Overall, 3-month mortality was 34%. Independent predictive factors of 3-month mortality were MELD score, serum sodium, and uNGAL levels at diagnosis, but not presence or stage of AKI.

Conclusions: In patients with cirrhosis and infections, measurement of urinary NGAL at infection diagnosis is useful in predicting important clinical outcomes, specifically persistency and type of AKI, development of a second infection, and 3-month mortality.

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Keywords: Biomarkers; NGAL; Bacterial infections; Hepatorenal syndrome; Cirrhosis; Kidney failure; AKI.

Received 29 November 2013; received in revised form 4 February 2014; accepted 25 February 2014; available online 5 March 2014

* Corresponding author. Address: Liver Unit, Hospital Clínic, Villarroel, 170, 08036 Barcelona, Spain.

E-mail address: pgines@clinic.ub.es (P. Ginès).

† The authors contributed equally to this work.

Introduction

Bacterial infections are a very common complication of patients with cirrhosis that are associated with a high morbidity and mortality [1–5]. Among the complications associated with infections, impairment of kidney function is particularly relevant from a clinical perspective. Most importantly, studies have unequivocally demonstrated that development of kidney impairment during the course of bacterial infections is associated with impaired prognosis regardless of the criteria used to define impairment of kidney function [6–9].

An interesting issue in bacterial infections in cirrhosis is whether the use of kidney biomarkers can be helpful for the diagnosis and management of kidney impairment developing in this setting. The potential use of such biomarkers would be particularly important for early identification between transient and persistent impairment of kidney function as well as for the differential diagnosis of the etiological cause [6,10–12]. Moreover, persistent kidney impairment in cirrhotic patients may be due to different causes, specifically intrinsic-AKI or type-1 HRS [13,14]. Differentiation between these two clinical causes is relevant because treatment is different: circulatory support and/or renal replacement therapy in the former and terlipressin and albumin in the latter [2,3,13]. In this regard, recent studies in cirrhosis have shown that measurement of neutrophil gelatinase-associated lipocalin (NGAL), a kidney biomarker overexpressed in

conditions of kidney injury, in urine may be helpful in the assessment of the cause of kidney impairment in an unselected population of hospitalized patients with cirrhosis [15,16]. However, its role in patients with cirrhosis and bacterial infections is unknown. On this background, the current study was undertaken to evaluate prospectively the role of uNGAL in determining the cause and outcome of AKI as well as its potential value in prognosis assessment in these patients.

Patients and methods

Population and study protocol

All consecutive patients with cirrhosis with a bacterial infection either at admission or who developed it during hospitalization at the Hospital Clinic of Barcelona from November 2011 to March 2013 were eligible for inclusion in this prospective study. Exclusion criteria were: (1) chronic hemodialysis before admission; (2) previous liver and/or kidney transplantation; (3) hepatocellular carcinoma outside the Milan criteria or any other advanced malignancy; (4) lack of informed consent; and (5) patients with urinary tract infection; these latter patients were excluded because uNGAL levels are increased in these patients and may therefore not reflect and impairment of kidney function [16,17]. A total of 170 consecutive patients were screened and 38 were excluded. Therefore, 132 patients constitute the study population.

At admission, a detailed medical history was recorded. Standard laboratory tests were measured at admission and at regular intervals during hospitalization. Identification of the source of infection was performed using standard diagnostic procedures. Antibiotic therapy was given according to previously described protocols [13].

A fresh urine sample was collected, usually by spontaneous voiding, at the time of diagnosis of the infection (median time between infection diagnosis and collection of urine sample was of 1 day). Standard urinalysis was performed in this sample and a fraction of it was centrifuged at 1000 rpm and the supernatant stored at −80 °C for later measurement of NGAL. In a fraction of patients urine samples were also collected at days 3 and 7. Moreover, plasma samples were collected for measurement of plasma renin activity (PRA) and plasma concentration of aldosterone, and norepinephrine at diagnosis and at day 7.

After discharge, patients were followed-up in the outpatient clinic for at least 3 months. All patients gave written informed consent and the study was approved by the Institutional Review Board.

Definitions

The diagnosis of cirrhosis and bacterial infections was done using previously reported definitions (see Supplementary Patients and methods).

Acute kidney injury

Impairment of kidney function was defined using the AKIN criteria [18], evaluated in intervals of 48–72 h throughout hospitalization, as an increase in serum creatinine of ⩾0.3 mg/dl or ⩾50% over the baseline value obtained in the previous 48–72 h. For the diagnosis of AKI at admission the value used as baseline was the most recent stable serum creatinine value available within the previous 3 months. This was done because most patients admitted to hospital with bacterial infections have already impairment of kidney function at admission [8,19]. The majority of patients included in the study (80%) had been followed-up in the outpatient clinic and therefore had pre-admission serum creatinine values available. If preadmission values were not available, the baseline value used was the first value at admission to hospital.

AKI was graded in stages 1 to 3 [18]. Stage 1 was further categorized in two groups: stage 1a, if peak serum creatinine during hospitalization was equal to or lower than 1.5 mg/dl, and stage 1b, if peak serum creatinine during hospitalization was greater than 1.5 mg/dl, according to recently published studies [20,21]. AKI was considered transient if serum creatinine returned to values not greater than 0.3 mg/dl over baseline within a 72 h period after diagnosis [10–12]. If patients developed more than one episode of AKI during hospitalization, only the first episode was considered for the current analysis. For management of AKI see Supplementary data.

Analytical methods

The urinary concentration of NGAL was measured using NGAL ELISA kit (Bioporto, Gentofte, Denmark). Coefficients of inter-assay and intra-assay variation were 12.6% and 3.4%, respectively. Normal values of uNGAL in a group of 20 healthy subjects were 35 (10–52) μg/g of creatinine (median and IQ range). See Supplementary data for other analytical measurements.

Statistical analysis

See the Supplementary data.

Results

Characteristics of patients

The characteristics of patients at diagnosis of the infection are shown in Table 1. Most patients had advanced cirrhosis, as indicated by high Child-Pugh and MELD scores. Forty-seven of the 132 patients (36%) required ICU care either at admission or during hospitalization. The most common type of infection was SBP followed by pneumonia and skin and soft tissue infection, which accounted for more than half of the infections (Supplementary Table 1).

Frequency, characteristics, and outcome of acute kidney injury

Sixty-five (49%) of the 132 patients developed AKI during hospitalization. AKI was already present at diagnosis of infection in 47 patients (72%); in the remaining 18 patients it developed in the following days after infection diagnosis (median 2 days; range: 1–6 days). At diagnosis of AKI, 43 patients had stage 1 (15 stage 1a and 28 stage 1b), 14 patients stage 2, and 8 patients stage 3. Twenty of the 65 patients had progression of AKI during hospital stay: two patients with stage 1a progressed to stage 1b, 10 patients with stage 1b progressed to stage 2 or 3 (5 patients each), and 8 patients with stage 2 progressed to stage 3. Two patients from stage 3 required dialysis later in hospitalization. Peak serum creatinine values for the different subsets of patients were as follows: no-AKI: 1.1 ± 0.5 mg/dl, AKI stage 1a: 1.2 ± 0.2 mg/dl, stage 1b: 2.0 ± 0.5 mg/dl, stage 2: 2.6 ± 0.7 mg/dl, and stage 3: 4.5 ± 1.9 mg/dl. Supplementary Fig. 1 shows mean serum creatinine values throughout hospitalization in all patients classified according to absence or presence of AKI and the maximum AKI stage reached.

Table 2 shows the comparison of baseline characteristics at diagnosis of the infection in patients categorized according to presence or absence of AKI. Patients with AKI had more advanced cirrhosis, as indicated by higher frequency of complications before the index hospitalization, more severe impairment of liver, kidney, and circulatory functions, greater severity of the infection, and higher frequency of health-care associated or nosocomial infections (of note, almost two thirds of patients – 61% – with health-care associated or nosocomial infections developed AKI). Interestingly, presence of chronic kidney impairment and treatment with beta-blockers before hospitalization were also associated with an increased frequency of AKI. In multivariate analysis, independent factors associated with AKI were MELD score and plasma renin activity.

In 40 out of the 65 patients (62%) AKI was persistent, while the remaining 25 patients had transient AKI. Fig. 1 shows serum

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