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Renal Impairment Is Frequent in Chronic Hepatitis C Patients Under Triple Therapy With Telaprevir or Boceprevir

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In clinical trials with telaprevir (TLV) and boceprevir (BOC) renal impairment was not reported as a relevant adverse event. The PAN study is a noninterventional study enrolling patients treated with peginterferon alfa-2a/ribavirin (PEG/RBV) with or without TVL or BOC. Here we restrict the analysis to hepatitis C virus genotype 1 patients having completed 12 (n = 895) or 24 weeks (n = 591) of treatment. For estimation of glomerular filtration rate (eGFR) the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was chosen. Patients on TLV 38/575 (6.6%) and BOC 10/211 (4.7%) more frequently experienced a decrease in eGFR to <60 mL/min compared to patients on PEG/RBV 1/109 (0.9%) ($P < 0.05$). Risk factors associated with eGFR <60 mL/min in multiple logistic regression analysis were age ($P < 0.001$), arterial hypertension ($P < 0.05$), higher serum creatinine at baseline ($P < 0.001$), and being on triple therapy with TLV or BOC ($P < 0.01$). Patients with an eGFR of <60 mL/min had a lower absolute mean hemoglobin at week 12 compared to patients with an eGFR >60 mL/min (9.7 g/dL ± 1.4 g/dL versus 11.0 g/dL ± 1.7 g/dL) ($P < 0.001$). Most patients on TLV with a decrease of eGFR <60 mL/min showed a marked improvement in renal function after discontinuation of TLV. *Conclusion*: Renal impairment has not been reported as a safety signal in clinical trials with TVL or BOC. However, in this large cohort including patients with risk factors for renal impairment a marked decline in renal function was observed in about 5% of patients on triple therapy. In addition to being a safety concern, substantial ribavirin dose reductions have to be considered in these patients, as anemia was more pronounced in patients with impaired renal function. (HEPATOLOGY 2014;59:46-48)

Dual treatment of chronic hepatitis C virus (HCV) with peginterferon alfa-2a/ribavirin (PEG/RBV) is characterized by numerous adverse events. However, renal impairment has not been identified as part of the adverse event profile. Until recently, experience with telaprevir (TLV) and boceprevir (BOC) was based exclusively on clinical trials in selected patients. In these trials renal impairment was not reported as a safety issue.[1-4] However, in the French early access program, cases of renal failure were observed.[5] In the present study we analyzed the development of estimated glomerular filtration rate (eGFR) in patients treated with interferon-based therapies with or without the addition of BOC or TLV in a large cohort of patients enrolled in a noninterventional study.

Materials and Methods

The PAN study is a noninterventional study conducted by the Association of German Gastroenterologists in Private Practice (bng) in collaboration with

Abbreviations: BOC, boceprevir; CKD-EPI equation, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; TLV, telaprevir.

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Roche. Patients treated with dual therapy consisting of PEG/RBV or triple therapy with TLV or BOC are eligible. The treatment decision is made by the physician in charge. In total, 2,850 treated patients are enrolled. Here we restrict the analysis to HCV genotype 1 patients having at baseline an eGFR >60 mL/min. Patients with human immunodeficiency virus (HIV) coinfection were excluded from the analysis. Erythropoietin is not approved in Germany for the treatment of anemia associated with HCV therapy and was not used in the cohort. Two datasets of patients were selected, the first having completed at least 12 weeks of treatment (n = 895) and the second at least 24 weeks of treatment (n = 591).

The 12-week analysis assesses the effect of treatment initiation on eGFR, whereas the 24-week dataset was chosen to assess the possibility of reversibility of the effect of TLV therapy on eGFR after the discontinuation of TLV after 12 weeks of triple therapy. Due to the longer treatment duration of the triple combination, there are no sufficient data yet for patients reaching the end of treatment for BOC.

In the cohort creatinine results were recorded at baseline, week 12, week 24, and every 12 weeks thereafter until 24 weeks after end of treatment. No documentation of urine analysis was recorded.

The eGFR was calculated with the recently presented Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which may be best suited to reflect changes of eGFR in patients with normal or mildly impaired renal function.[6] For statistical analysis in a first step, univariate regression analysis was used. All variables reaching $P < 0.05$ in the univariate analysis were entered in a multiple logistic regression analysis. Software used was IBM SPSS Statistics v. 21.0.0.0.

Results

Overall, 895 patients were included, 575 on TLV, 211 on BOC, and 109 on dual therapy. Baseline demographics are shown in Table 1. As expected, HCV genotype 1 patients treated with dual therapy were younger, had more frequently low level HCV-RNA, and had a lower proportion of patients with diabetes mellitus or arterial hypertension, reflecting a selection for variables associated with better treatment outcome or being naïve to HCV therapy.

Table 1. Baseline Demographics

	Dual Therapy N = 109	Boceprevir N = 211	Telaprevir N = 575
Mean age (years)	41.6 ± 11.5	48.9 ± 10.5	48.5 ± 11.0
Female sex	39%	39%	33%
Body mass index (kg/m^2), mean ± SD	25.4 ± 4.2	27.0 ± 5.0	26.4 ± 4.4
Smoking	53%	50%	41%
Median creatinine (mg/dL)	0.8	0.8	0.8
eGFR >60-90 ml/min	25%	31%	24%
eGFR >90 ml/min	75%	69%	76%
ALT U/L mean ± SD	110 ± 63	89 ± 61	97 ± 81
HCV-RNA ≤400,000 IU/mL	49.5%	28.6%	23.4%
Arterial hypertension	9%	26%	16%
Diabetes mellitus	2%	9%	7%
APRI score >1.5	12%	17%	18%

At week 12 a decrease of eGFR to <60 mL/min in patients with >60 mL/min at baseline was observed in 49/895 (5.5%) patients overall. Patients on TLV 38/575 (6.6%) and BOC 10/211 (4.7%) experienced more frequently a decrease in eGFR to <60 mL/min compared to patients on PEG/RBV 1/109 (0.9%) ($P < 0.05$).

Risk factors associated with eGFR <60 mL/min corresponding to renal insufficiency stage 3 were age ($P < 0.001$), arterial hypertension ($P < 0.001$), diabetes mellitus ($P < 0.05$), a higher serum creatinine at baseline ($P < 0.001$), and being on triple therapy with TLV or BOC ($P < 0.05$). There was no association with baseline hemoglobin, smoking, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), HCV-RNA, HCV treatment history, sex, APRI score, or comedications including nonsteroidal antiinflammatory drugs. In the multiple regression analysis age ($P < 0.001$), a higher creatinine at baseline ($P < 0.001$), being on triple therapy with TLV or BOC ($P < 0.01$), and arterial hypertension ($P < 0.05$) remained significantly associated with a decrease in eGFR to <60 mL/min.

Patients with a drop of eGFR to <60 mL/min had a lower absolute mean hemoglobin at week 12 with 9.7 g/dL ± 1.4 g/dL compared to 11.0 g/dL ± 1.7 g/dL

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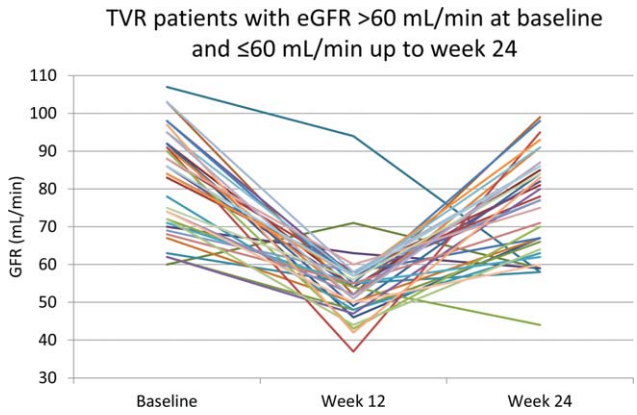

Fig. 1. Course of eGFR in individual patients treated with TLV until week 12 with eGFR >60 mL/min at baseline and eGFR ≤60 mL/min up to week 24.

in patients with an eGFR >60 mL/min ($P < 0.001$). The absolute decrease in hemoglobin was also different, with 5.3 g/dL ± 1.3 g/dL compared to 3.8 g/dL ± 1.6 g/dL, respectively ($P < 0.001$).

In the second analysis a smaller patient subset which had already reached week 24 of therapy was assessed. In total, 591 patients were included, 398 on TLV, 113 on BOC, and 80 on dual therapy. In this subset a decrease of eGFR to <60 mL/min at week 12 was observed in 33/398 (8.3%) patients on TLV, 4/113 (3,5%) on BOC, and 1/80 PEG/RBV (1.3%) ($P < 0.05$). At week 24 eGFR <60 mL/min was observed in 5/398 (1.3%) in the TLV group, who were at this timepoint on dual therapy with PEG/RBV, as the approved treatment duration with TLV is limited to the first 12 weeks of therapy. An eGFR of <60 mL/min was observed at week 24 in 5/113 (4.4%) patients on BOC and 1/80 patients on PEG/RBV (1.3%) ($P < 0.05$). The time course of eGFR from week 12 to 24 in patients on TLV therapy for the first 12 weeks and with a reduction in eGFR <60 mL/min is shown in Fig. 1. In most patients the decrease in eGFR <60 mL/min occurred in the first 12 weeks and was reversed until week 24.

Discussion

Renal impairment has not been reported as a safety signal in clinical trials with TLV or BOC. This may be due to the selected patient population in clinical trials frequently excluding patients with comorbidities or specific comedications. In this large cohort a substantial proportion of patients had risk factors for renal impairment such as older age, arterial hypertension, or diabetes mellitus. All these variables were associated with a marked decrease in eGFR to <60 mL/min at least in univariate analysis. In addition, being treated with TLV or BOC was an additional risk factor in univariate and multivariate logistic regression analysis. About 5% of patients on triple HCV therapy with BOC or TLV showed at least temporary renal insufficiency stage 3. For TLV it could be demonstrated that this is a reversible effect in the vast majority of patients. The improvement of renal function after discontinuation of the HCV protease inhibitor argues strongly for a causal relationship. However, the pathophysiologic mechanism remains unknown to date and should be subject to further research. The involvement of both TLV and BOC may indicate a class effect, at least for the first generation of HCV protease inhibitors.

In addition, a more pronounced anemia was observed in patients with decreased renal function. This is likely due to an accumulation of ribavirin due to an impaired renal elimination. As a consequence, substantial ribavirin dose reductions should be considered in these patients.

A limitation of this study is the lack of data on urine, in particular proteinuria, which may have given additional information on the origin of the renal impairment, i.e., tubular, glomerular, or combined.

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