

# Response Guided Treatment with Telaprevir or Boceprevir in End Stage Renal Disease Patients with Hepatitis C Genotype 1

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## ABSTRACT

**AIM:** To evaluate and characterize the feasibility, tolerability and efficacy of triple combination therapy with either telaprevir (TPR) or boceprevir (BPR).

**METHODS:** We treated 16 genotype 1 HCV patients with ESRD, awaiting renal transplantation at two centers. All patients received pegylated-interferon (P), ribavirin (R), and either boceprevir or telaprevir. All patients with BPR received a 4-week lead-in whereas those with TPR received no lead-in. Data was collected throughout the patients' treatment course including viral load, dose modification and complications of therapy.

**RESULTS:** Baseline characteristics of the cohort included mean age of 56 years, 75% male, 56% African-American, 63% genotype 1a HCV, 38% with cirrhosis and 69% treatment naïve. eRVR was achieved in 38% (56% in TPR and 14% BPR) with SVR achieved in 44% (33% in TPR and 57% BPR). Over 70% of patients required epoetin for anemia whereas 22% in TPR required blood transfusions. No patients in either TPR/BPR treatment cohorts

discontinued therapy due to side effects.

**CONCLUSION:** We evaluated and analyzed the efficacy of telaprevir and boceprevir based regimens in the treatment of hepatitis C in patients with end stage renal disease. Triple therapy, irrespective of regimen, can attain successful viral eradication with minimal adverse effects.

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**Key words:** Hepatitis C; End-stage renal disease; Boceprevir; Telaprevir

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## INTRODUCTION

Chronic hepatitis C HCV affects more than 150 million (3%) of the world's population with an estimated progression to cirrhosis as high as 20%<sup>[1]</sup>. HCV has significance in the field of kidney transplantation, as up to 15% of kidney transplant patients are afflicted with hepatitis C (HCV)<sup>[2]</sup>. Patients with end-stage renal disease (ESRD) and concomitant HCV have higher rates of morbidity and mortality both before and after kidney transplant compared to uninfected controls<sup>[3-4]</sup>. Kidney graft recipients with HCV have an increased risk of developing diabetes mellitus, membranoproliferative glomerulonephritis (MPGN) and graft loss. Although HCV eradication may improve survival of ESRD patients with CHC, antiviral therapy remains challenging in this population.

Based on Kidney Disease Improving Global Outcomes (KDIGO) recommendations, patients that meet criteria for kidney

transplant can be considered candidates for HCV therapy due to the significant survival advantage with transplant<sup>[5]</sup>. A prior meta-analysis by Fabrizi *et al* evaluating HCV/CKD patients on dialysis demonstrated a relative risk (RR) for all-cause mortality of 1.34 with more significant risk of liver-related mortality of 3.75<sup>[6]</sup>. Successful treatment and eradication of HCV prior to kidney transplant lead to reduction in graft failure, incidence of diabetes mellitus and HCV-associated glomerulonephritis<sup>[7]</sup>. Interferon based therapy is generally contraindicated in kidney transplant recipients due to the high risk of graft rejection<sup>[8]</sup>.

Until recently, HCV patients with ESRD were treated with the combination of pegylated interferon and ribavirin. Since ribavirin is not efficiently eliminated by dialysis, early risks of significant anemia led to suggestions for use in lower fixed doses to increase SVR rates<sup>[9]</sup>. The combination of pegylated-interferon and low dose ribavirin demonstrated SVR rates of approximately 30%, however, most studies show a high dropout rate (up to 25%) mainly due to anemia<sup>[10-12]</sup>.

Limited data is available on the use of newly available protease inhibitor therapy (boceprevir or telaprevir) in combination with pegylated interferon and ribavirin. The addition of a protease inhibitor has increased SVR rates up to 70% in patients without ESRD<sup>[13]</sup>. Concern for protease inhibitor related side effects to include drug interactions and increased risk of anemia has limited widespread use in ESRD patients<sup>[14-15]</sup>. Preliminary studies have shown the feasibility of using triple combination therapy for viral eradication in conjunction with adequate tolerability, especially with respect to anemia management<sup>[16-18]</sup>.

Our study evaluated the efficacy of triple drug response guided therapy on HCV Genotype 1 patients with ESRD on the waitlist for kidney or combined liver/kidney transplantation. We wanted to further evaluate and characterize the feasibility and tolerability with either telaprevir or boceprevir based regimens.

## MATERIALS AND METHODS

We performed a retrospective study approved by the institutional review boards at two transplant centers, Methodist Specialty and Transplant Hospital (MSTH), San Antonio, Texas and University of Miami, Florida. We included patients who underwent hepatitis C treatment prior to renal transplantation.

### Patient Protocol

Sixteen patients with serological evidence of Hepatitis C (Genotype 1) and CKD actively on the waitlist for either kidney transplantation or combined kidney/liver transplantation were included. Data was obtained from a combination of a computerized database and paper and electronic charts. The study obtained IRB approval from Methodist Liver Transplant Center in San Antonio, TX and University of Miami in Miami, FL.

All patients received pegylated interferon alpha 2a (P), ribavirin (R) and either boceprevir (BPR) 800 mg every eight hours or telaprevir (TPR) 750 mg every eight hours. All patients treated with BPR received 1-month lead-in, P 180 mcg weekly and R 200 mg three times weekly whereas those treated with TPR received no lead-in, P 135 mcg weekly and R 200 mg daily, twice weekly or three times weekly at the discretion of the clinician (based on baseline hemoglobin).

## RESULTS

### Baseline Characteristics

Sixteen patients with end-stage renal disease (ESRD) and

concomitant chronic hepatitis C (CHC) were evaluated at two academic institutions based on treatment modality: 9 with telaprevir (TPR cohort) and 7 with boceprevir (BPR cohort). The average age was 56.0 years for the TPR cohort vs 54.0 years for the BPR cohort. The patients were predominantly male in both cohorts (78% in TPR cohort vs 71% in BPR cohort). African-American race was most frequent (67% in TPR cohort vs 43% in BPR cohort). All patients were listed for kidney transplantation and in addition 31% were considered for combined kidney-liver transplant. Cirrhotic patients made up approximately 38% of all patients (33% in TPR cohort vs 43% in BPR cohort). All baseline characteristics are summarized in table 1.

**Table 1** Review of baseline characteristics in cohorts.

Demographic Characteristics	Telaprevir Cohort	Boceprevir Cohort
Number of patients	9	7
Age, yrs	56.0	54.0
Gender		
Male	7	5
Female	2	2
BMI		
Normal	3 (33)	1 (14)
Overweight	3 (33)	1 (14)
Obese	3 (33)	5 (71)
Ethnicity		
African-Americans	6 (67)	3 (43)
Hispanics	3 (33)	2 (29)
Caucasian	0	2 (29)
Cause of ESRD		
Hypertension	7 (78)	4 (57)
Diabetes	3 (33)	0
Lupus Nephritis	1 (11)	1 (14)
FSGS	1 (11)	1 (14)
PCKD	1 (11)	0
Liver Transplant Candidate	3 (33%)	3 (43)

Categorical variables are described as *n* (%); BMI: Body Mass Index; ESRD: end-stage renal disease; FSGS: focal-segmental glomerular sclerosis; PCKD: polycystic kidney disease.

### Treatment Characteristics and Regimens

All patients were infected with HCV genotype 1 with a majority having subtype genotype 1a (67% in TPR cohort vs 57% in BPR cohort). Most patients (69%) were treatment naïve with only a small proportion of patients with prior non-response to peg-interferon (P) and ribavirin (R) therapy (6%). With respect to IL 28B analysis, 44% in the TPR cohort and 29% in the BPR cohort had CT and TT, respectively (4 patients did not undergo testing).

All patients underwent treatment with protease inhibitor therapy in combination with P and R up to 48 weeks based on established response guided therapy rules. The majority of patients underwent therapy with telaprevir (56%) versus 44% with boceprevir therapy. All patients who underwent boceprevir therapy undertook a 4-week lead-in with P and R. All patients in the TPR cohort were started on P 135 mcg and majority with R 200 mg three times weekly. The majority in the BPR cohort were started on P 180 mcg with R 200 mg three times weekly.

### Treatment Responses

Thirty-eight percent of patients achieved an eRVR, defined as negative viral load at week 4 for TPR and week 8 for BPR (56% with TPR vs 14% with BPR). With respect to end of treatment response (EOT), 63% of patients were virus negative (44% in TPR cohort vs 86% in BPR cohort). 44% of patients achieved an SVR (33% in TPR cohort vs 57% in BPR cohort). Pegylated-interferon dose reductions occurred in 2 patients (1 in TPR cohort

and 1 in BPR cohort) and both required Neupogen therapy due to agranulocytosis. Ribavirin dose reductions were not necessary in telaprevir-treated patients compared to 33% in the boceprevir-treated patients. Treatment characteristics and responses are summarized in table 2.

**Table 2** Review of treatment characteristics and results of therapy in both cohorts.

Treatment Characteristics and Responses	Telaprevir Cohort	Boceprevir Cohort
Number of patients	9	7
Genotype		
1a	6 (67)	4 (57)
1b	3 (33)	3 (43)
Treatment History		
Naive	6 (67)	5 (72)
Prior Relapse	2 (22)	1 (14)
Prior Non-Responder	1 (11)	0
Unknown	0	1 (14)
IL28b Genotype		
CT	4 (44)	2 (29)
TT	4 (44)	2 (29)
Unknown	1 (12)	3 (42)
Stage of Liver Disease		
0	3 (33)	1 (14)
1	3 (33)	1 (14)
2	0	0
3	0	2 (29)
4	3 (33)	3 (43)
eRVR	5 (56)	1 (14)
EOT response	4 (44)	6 (86)
SVR (12 weeks post)	3 (33)	4 (57)

Categorical variables are described as *n* (%); IL28b: interleukin 28b; eRVR: extended rapid virologic response; EOT: end of treatment; SVR: sustained virologic response.

### Safety of Therapy and Management

Most patients in the telaprevir-treated group required erythropoietin (EPO) for anemia compared to 67% in the boceprevir-treated group. One patient in each of the treatment groups required hospitalization for anemia. Three patients required blood transfusions due to symptomatic anemia (2 in the TPR cohort and 1 in the BPR cohort). One patient developed hepatic-decompensation while on therapy in the telaprevir group. With respect to adherence, one patient was discontinued early on therapy due to non-compliance and one patient was lost to follow-up after completion of therapy. No patients in the cohort discontinued therapy due to adverse effects. Safety and management are summarized in table 3.

**Table 3** Review of treatment complications with both cohorts.

Safety Characteristics and Management	Telaprevir Group	Boceprevir Group
RBV dose reduction	0	2 (29)
IFN dose reduction	1 (11)	1 (14)
Neupogen therapy	2	1
Thrombocytopenia	1 (11)	0
Promacta therapy	1	0
Anemia Management		
EPO	7 (78)	5 (71)
Blood Transfusion	2 (22)	1 (14)
Miscellaneous Complications		
Hepatic Decompensation	1 (11)	0
Non-Compliance	1 (11)	0
Pneumonia	0	1 (14)
Dehydration	1 (11)	0
Fistula Infection	1 (11)	0

Categorical variables are described as *n* (%); RBV: ribavirin; IFN: pegylated interferon-alpha2a; EPO: erythropoietin.

## DISCUSSION

Several early studies demonstrated the efficacy of using pegylated-interferon and ribavirin combination therapy in the treatment of HCV in CKD<sup>[10-12,19]</sup>. A recent meta-analysis of combined antiviral therapy confirmed the ease and efficacy of therapy in CKD patients on hemodialysis<sup>[20]</sup>. Limited studies have been available evaluating use of new protease inhibitor therapy with interferon and ribavirin.

A majority of the previous literature available for HCV treatment in dialysis patients involves use of interferon monotherapy or interferon with ribavirin. Interferon monotherapy had a significant range with respect to SVR from 20-71% but was complicated by high drop-out rates due to medication-induced side effects<sup>[21-23]</sup>. The use of combination pegylated-interferon and ribavirin demonstrated better SVR rates than previously noted with interferon monotherapy. Giguere *et al* demonstrated 76% SVR rate in combination therapy and has been correlated with similar studies<sup>[24-25]</sup>. Unfortunately, limited literature is available on the use of direct acting anti-viral therapy (such as telaprevir or boceprevir) in dialysis patients<sup>[26-27]</sup>. However, a single dose pharmacokinetic therapy in ESRD patients on dialysis demonstrated equivalent bioavailability and maximum concentration of boceprevir compared to healthy subjects<sup>[28]</sup>. Active clinical trials are being undertaken.

Our study effectively demonstrated the use of protease inhibitor therapy in this population. We were able to show that 44% of patients on triple therapy achieved viral eradication, irrespective of the form of protease inhibitor therapy. The majority of patients were able to successfully complete >24 weeks of therapy with minimal complications. In comparison to prior studies, our SVR is considerably lower than conventional therapy with pegylated-interferon and ribavirin therapy. We suspect our small population size may have played a major factor in the lack of efficacy.

The greatest challenge in the use of protease inhibitor therapy has been anemia. In registration trials and in clinical practice with use of boceprevir or telaprevir, anemia was one of the most significant side effects. Pooled analysis of the pivotal telaprevir trials showed approximately 36% of patients with hemoglobin levels <10 g/dL<sup>[28,29]</sup>. Similar findings were demonstrated in the SPRINT-1 and SPRINT-2 trials for boceprevir as approximately 49% of treated patients developed anemia<sup>[13,30]</sup>. The role of erythropoietin has never been formally evaluated with protease inhibitors but such therapy has brought significant benefits in limiting anemia-related side effects<sup>[13]</sup>.

The majority of our patients developed anemia, which was well controlled with the use of erythropoietin. However, two patients required hospitalization for anemia related side effects and both required blood transfusions. Despite anemia, the majority of patients completed triple therapy and no side-effect related discontinuation of therapy occurred. Only one patient was unable to complete therapy due to non-compliance with medications. All patients with anemia were successfully treated without any major complications and had effective viral eradication. One patient on the combined liver-kidney transplant list who had successful eradication of HCV with triple therapy had fibrosis regression, improvement in portal hypertension and was able to successfully undergo isolated kidney transplantation without the need for liver transplantation.

One of the significant limitations to our study, again, was the limited number of patients evaluated. However, this is the largest cohort study retrospectively evaluating the treatment and management of ESRD patients undergoing hemodialysis with CHC (genotype 1) with boceprevir and telaprevir. We demonstrated that triple therapy, irrespective of regimen, could offer viral eradication with successful

management of anemia.

HCV in ESRD patients form special cohorts who are considered a difficult-to-treat group. Although there is a surge of evolving direct acting anti-viral therapy (DAA) data in non-dialysis patients, there is comparatively limited data in dialysis patients. Our study has demonstrated the efficacy and safety of first generation anti-viral therapies (boceprevir/telaprevir). Further studies with interferon-free and perhaps ribavirin-free regimens are still in preliminary phases of clinical trials and are highly anticipated in the near future.

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