

## Syncope during boceprevir treatment in hepatitis C

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Dear Editor:

Recently, the standard of care (SoC) of chronic hepatitis C virus (HCV) infection has changed, and HCV treatment has entered a new era with the introduction of direct-acting antiviral agents (DAAs). Combination therapy with pegylated interferon (pegIFN) and ribavirin (RBV) and the two first generation NS3/4A protease inhibitors (PI) –telaprevir (TVR) and boceprevir (BOC)– has been approved in many countries.<sup>1-3</sup> Although these combinations significantly increase sustained virological response (SVR) rates, they also increase adverse events rates.<sup>4-7</sup> Previously well known adverse events related to pegIFN/RBV increases their frequency and severity, and new adverse events related to PIs develop. Anemia and dysgeusia are more frequent in patients treated with BOC and anemia, pruritus, rash and anorectal symptoms are more frequent in patients treated with TVR, when compared with PegIFN/RBV alone.<sup>4-7</sup> With PIs therapy incorporated in clinical practice, new adverse events may be expected. Another new concern appears with HCV therapy triple therapy: drug-drug interaction; with the risk of increasing adverse events and decreasing SVR rates.

Treatment with PegIFN/RBV has not been associated with significantly cardiac morbidity, if patients are adequately selected. Hypertension, hypotension, arrhythmias, chest pain, myocardial infarction, and strokes have been observed in patients treated with PegIFN/RBV. Because these are spontaneous reports, estimates of frequency cannot be made, and a causal relationship between

PegIFN-based therapies and these events is difficult to establish.<sup>8,9</sup> Syncope may be associated to concomitant use of PDE-5 inhibitors and PIs.<sup>10</sup> We report the first case of severe syncope in a patient treated with BOC based triple therapy.

The patient is a cirrhotic 64 years old male, partial responder to previous treatment infected with genotype 1b. He never had complications of cirrhosis and he was taking propranolol 20 mg TID for 4 years, for variceal bleeding prophylaxis. His baseline viral load was 824,000 IU/mL (5,9 log). He began treatment with PegIFN  $\alpha$ 2a 180  $\mu$ /week (he developed rash with PegIFN  $\alpha$ 2b in a previous treatment) and RBV 1,200 mg/day. At week 4, after lead in phase it reduced to 7.430 IU/mL (3,8 log) and boceprevir 800 mg TID was initiated; and at week 8, viral load was 137 IU/mL (2,4 log). At week 11 of treatment he developed 3 episodes of syncope. The first one recovered spontaneously, and propranolol was suspended. The second required admission to the ICU for 36 hours, since he suffered head trauma. And the third one occurred at the office on week 12 consultation, and was witnessed by the treating physician. Each episode was similar: it began with nausea, sweating, hypotension (systolic blood pressure of 50 mmHg), bradycardia (40 beats per minute) and loss of consciousness. He recovered after 2 to 3 min, with all parameters returning to normal values. After the third episode triple therapy was stopped. He also developed anemia (hemoglobin at week 12 was 8.5 mg/dL), thrombocytopenia (platelets count at week 12 was 26.000/mm<sup>3</sup>) and neutropenia (neutrophils count at week 12 was 770/mm<sup>3</sup>). A brain CT scan, an EKG, an echocardiography with Doppler and a 24 h EKG recording were normal at the time of evaluation. Propranolol was reinitiated 2 weeks after the last episode. Three month after stopping therapy, his is asymptomatic and syncope never recurred.

This is the first report of severe cardiac toxicity related to BOC based therapy. BOC appeared to be responsible for it. Cirrhosis and severe hematology

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gic toxicity may have played a role. It appears that propranolol is not related to the adverse event. In the future, new adverse events not reported in clinical trials, may appear. It is important that new adverse events are reported, so every physician may be aware of them.

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