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Letter to Editor

Cardiac Toxicity Associated with HCV Direct Antiviral Agents

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Dear Editor,

Hepatitis C treatment is evolving from interferon-based therapy (IFN) 1-2 to direct antiviral agents (DAA), which have been shown to be highly effective with very few adverse events,[1,2] so, unlike interferon,[3] they can be safely administered, without growth factors, even in the presence of thrombocytopenia and anemia,[2,4] but may have some dangerous extra-hematological adverse effects, currently little known. In 2015 the Food and Drug Administration and the European Medical Agency added information to the Harvoni (ledipasvir / sofosbuvir) and Sovaldi (sofosbuvir) labels about the serious slowing of the heart rate of amiodarone when taken in combination with another direct acting antiviral for the treatment of hepatitis C infection. It is still unknown why amiodarone together with DAAs can lead to heart-related events, yet FDA recommends heart monitoring in inpatient hospital setting for the first 48 hours in case of unavailable alternative options of treatment.[5,6]

After FDA published the warning about the bradycardia occurring during direct-acting antiviral (DAA) treatment, several concerns have arisen regarding cardiac toxicity, and a few cases of extreme bradycardia have been described. Furthermore, DAA therapy is often used in older population which have a higher risk of heart related diseases, and consequently of related adverse.[7]

We report a single center experience of four cases of arrhythmias in patients under DAA treatment that were not under therapy with amiodarone, and we retrospectively evaluated the clinical and pathological findings of the cases.

At the time of the analysis, we had enrolled a total of 110 patients undergoing DAAs therapy with electrocardiographic exam performed before DAAs therapy and did not show any alteration.

A first patient is a 69-year-old man infected with HCV genotype 1a. He was diagnosed with paroxysmal atrial fibrillation in 2012, and he was in treatment with aspirin, valsartan+ hydrochlorothiazide and flecainide. He had high grade hepatic fibrosis (14,5 kPa, F4 Metavir) by Fibroscan. He started the treatment with 3D+ Ribavirin (ombitasvir / paritaprevir / rit+dasabuvir+RBV scheme for 24 weeks) in April 2015 when he had a viremia of 816.793 UI/ml. In June, HCV-RNA was already undetectable in plasma samples. In July it was necessary to adjust the ribavirin dosage (800 mg/die) due to drug-induced anemia (Hb 12,7 mg/dl). In July he had a lypotimic episode and valsartan was reduced. In October he had an extreme bradycardia episode that led to a syncope requiring hospitalization. Even if the DAAs therapy was suspended, arrhythmias were so severe that the implantation of a double chamber pace-maker (PMK) was needed. Despite the DAA adverse effects, the SVR12 (i.e., the absence of detectable plasma HCV RNA 12 weeks after completion of treatment) was achieved. An interaction with flecainide cannot be ruled out, but the persistence of bradycardia after DAA suspension raises concerns about a more direct conduction system toxicity.

The second one is a 75-year-old woman, positive for HCV infection since 1995, genotype 1b. She also had sinusal bradycardia, high blood pressure, and favism. She was under treatment with perindopril, nebivolol, and colecalciferol. She started the treatment with DAAs in January 2016 (Daclatasvir + Sofosbuvir for 12 weeks) with a

viremia of 31.610 UI/ml. We observed the viremia dropping from 31.610 to 630 UI/ml at the end of the second week of treatment, and then it remained persistently suppressed. In February, the second month of therapy, she referred an episode of atrial fibrillation spontaneously reverted to sinus rhythm. In April, the last month of therapy, she referred to a similar episode of AF. We are now in the third month of follow up, and the viremia is still negative, therefore, the patient has obtained SVR12.

Patient n°3 is a 60-year-old man who had had HCV infection for 25 years, genotype 1b. He had a history of surgical procedures. He is a non-responder to previous PEG-IFN plus ribavirin therapy which lasted for 15 months, during which he did not have problems except for itching and an episode of syncope with urine loss few hours after the administration of IFN. The Fibroscan testing documented a stiffness of 6,3 kPa (Metavir F2), and he had an HCV viremia of 1.118.000. The patient had a diagnosis of arterial hypertension, so stress ECG and a Holter test were performed, resulting in being perfectly normal. He started the treatment for HCV with PEG-IFN+ribavirin+simeprevir for 12 weeks and then further 12 weeks with PEG-IFN+ribavirin in December 2015. During the second month of treatment, he was hospitalized because of a malignant syncope due to a total atrioventricular block. There was a danger of death so a PMK was implanted and the therapy definitively suspended. However, in December, the patient had no more HCV-RNA detectable in the bloodstream and, even if he had been under DAA treatment for just two months, the viremia was still negative with SRV12.

A last patient is a 58-year-old man, genotype 1b. He relapsed with the previous treatments with PEG-IFN and Ribavirin. He has diabetes mellitus type II treated with oral antidiabetic drugs and insulin. He had a high grade hepatic fibrosis measured through Fibroscan which documented a parenchymal stiffness of 61,8 kPa (F4 Metavir). He began the treatment with Sofosbuvir, Simeprevir, and Ribavirin (12 weeks) in April 2015. After one month of therapy, the HCV-RNA was undetectable in venous blood samples. The treatment was interrupted after only 46 days because of a myocardial infarction complicated with pericardial effusion and arrhythmia that required immediate coronary revascularization together with colchicine and corticosteroids, but the patient obtained SVR12.

All patients have had cardiac symptoms within the morning of the therapy administration, 2-3 hours after taking the DAA therapy. All patients stopped the treatment after having adverse, and all patients have reached the SVR12.

Out of 110 enrolled subjects treated with new DAA for hepatitis C, we had information on severe adverse events for four patients, so in 3.6% of our sample, a cardiac event perhaps correlated to new DAA has occurred. This is a clinical report of cardiac dysfunction associated with the treatment of chronic HCV infection. The first report of Ahmad et al.[8] showed six of thirty-four patients receiving IFN-free BMS-986094 regimes who reported cardiotoxic changes; pathological analysis revealed severe myocyte damage with elongated myofibrils without gross necrosis. In this observation of four cases of 110 treatments with new DAA, there is no pathologic analysis of the cardiac tissue since the correlation was realized after the events, and the biopsy was considered too invasive. However, the correlation between DAAs and an alteration in cardiac function was strong, given the occurrence of the cardiac problems soon after starting the new therapy, occurring all the cardiac events, including atrial fibrillation, in the morning after taking the pills. Cases of severe bradycardia and heart block have been observed when the DAAs were used in combination with amiodarone, with or without other heart rate lowering drugs. The mechanism is not established. The concomitant use of amiodarone was limited through the clinical development of sofosbuvir plus other DAAs. These cases are potentially life threatening, therefore amiodarone should not be used in patients with DAAs. When the concomitant use of amiodarone is necessary, patients are recommended to be closely monitored when initiating this treatment. Although the mechanism of action is still not clarified, DAAs are believed to be able to increase the concentrations of these drugs (amiodarone, disapiramide, flecainide, mexiletine, propafenone, quinidine), when administered orally, by inhibition of the intestinal CYP3A4.[9] Close monitoring and clinical caution are therefore recommended, especially when these antiarrhythmics are administered orally.

Although these patients did not have symptomatic heart failure, the frequency of, after

exposure, cardiac dysfunction suggests possible drug-related cardiotoxicity. In most cases, there was no significant abnormality on the pre-treatment surface ECG, but echocardiographic or Holter cardiac studies were not performed. By reviewing the symptoms of these four cases, it is possible to speculate that the DAA therapy has a particular sensibility with nerve fibers of the sinoatrial node and can interact with the cardiac electrical activity.

Anyway, the possible cardiac toxicity of DAAs should be confirmed by a systematic study, and if ascertained would require careful monitoring of patients to identify early changes in cardiac function.

Consent for publication. Written informed consent was obtained from the patients for publication of this Case report.

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