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Case Report

Adverse Effect to Ombitasvir / Paritaprevir / Ritonavir and Dasabuvir: A Case Report

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Abstract

Ombitasvir / paritaprevir / ritonavir and dasabuvir were approved by the European Medicines Agency (EMA) in 2014 for the treatment of adult patients infected with the Hepatitis C virus (HCV) genotype 1 and 4 and genotype 1, respectively. Concomitant administration of dasabuvir with ombitasvir / paritaprevir / ritonavir combines three Direct Acting Antivirals (DAA): dasabuvir, ombitasvir, paritaprevir and ritonavir that is not active against HCV. Dasabuvir is a non-nucleoside inhibitor-dependent RNA polymerase of HCV RNA encoded by the gene NS5B [1]; ombitasvir inhibits NS5A phosphoprotein; paritaprevir is an inhibitor of NS3 / 4A protease required for proteolytic cleavage and ritonavir increases the systemic exposure of paritaprevir [2]. Treatment should be continued for 12 or 24 weeks depending on the degree of fibrosis and viral genotype. The objective is the eradication of the virus, achieving a Sustained Virological Response (SVR), which is defined as an undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion [3]. Generally, these new DAA are much more effective and better tolerated than older treatments. The majority of Adverse Reactions (ADRs) reported were mild (grade 1 severity) [1,2]. This does not mean that other more serious ADRs can be associated with these treatments. We present the case of a 74- year- old woman with poliserositis related to these DAA.

Introduction

In Spain up to 2014, approved treatments for hepatitis C, consisted of "bitherapy" (interferon plus ribavirin for genotypes 1, 2, 3, 4, 5 and 6) or "triple therapy" (pegylated interferon, ribavirin and an inhibitor of HCV protease direct-acting antiviral first generation; boceprevir or telaprevir, only for genotype 1 VHC). Triple therapy was a very important turning point in the treatment of chronic HCV infection with a significant increase in the effectiveness of therapy permitting the cure of many patients, but at the cost of many side effects.

Since 2014, a new therapeutic arsenal (DAA) has been used for the treatment of hepatitis C. It aims to provide very high rates of cure in patients infected by any of the 6 types of genotypes and as far as possible, eliminate the interferon treatment regimens for the associated ADRs (heart failure, sepsis, leucopenia, depression, loss of vision, etc). Also, the duration of treatment with interferon and inconvenience posed by needing an injection each week was an important drawback. In many cases, the treatment with interferon was discontinued for these disadvantages and no cure target rates were obtained.

Generally, these new DAA are much more effective and better tolerated than older treatments. The majority of ADRs reported were mild (grade 1 severity). Insomnia, anemia, nausea, pruritus, asthenia and fatigue were the most commonly reported ADRs. However, these new antivirals should be subject to additional monitoring (pictogram of an inverted black color on the packaging of each drug) because they are newly-marketed. Any side effects not reflected in the product information must be reported in order to promote their dissemination.

Case Report

We present a case of poliserositis as a possible adverse effect of antiviral drug treatment. A 74- year-old woman was diagnosed with hypertension which was treated, with manidipine and irbesartan / hydrochlorothiazide. She also presented with hypothyroidism which was treated with levothyroxine and chronic HCV genotype 1b treated with antiviral ombitasvir / paritaprevir / ritonavir and dasabuvir. After two weeks of antiviral treatment, she came to the emergency room with symptoms of general discomfort, vomiting (especially at the beginning of treatment), weakness, fatigue, shortness of breath with progressive worsening, showing edema of lower limbs and a fever that had started a few days prior to her arrival. Upon arrival, she presented as tachypneic with a fever of 38°C and with tachycardia along with other laboratory parameters (hemoglobin: 11: leukocytosis

(17,70 • 103 / uL leukocytes). Complementary analytical tests which highlighted hypoxemia (pCO2 = 28 mmHg pO2 = 41 mmHg pH = 7,49 mmHg) were performed. Other laboratory parameters were: hemoglobin 8 g / dL, hematocrit 34.2%, platelets: 202.0 • 103 / uL; urea: 35 mg / dL; serum creatinine: 0.68 m / dL; Na+: 120m m / L, K+: 4 mM / L). As for cardiac markers, a brain natriuretic peptide value (NT Pro-BNP) of 1355.8 pg / mL was obtained. The HCV RNA was undetectable (<15 IU / mL). A chest radiograph showed bilateral interstitial infiltrate and a transthoracic Echocardiography (Ecott) showed pericardial effusion. Given the clinical picture compatible with poliserositis (simultaneous inflammation of several serous membranes: pleura, peritoneum, pericardium, etc.) as a possible adverse effect to antiviral medication, treatment was terminated and the patient was admitted to the Intensive Care Unit (ICU). Due to respiratory failure, broad-spectrum antibiotics therapy was started after extraction of cultures and serology. These analyses were subsequently confirmed as negative. The rheumatology department was consulted for a poliserositis study in light of autoimmune disease. Familial Mediterranean Fever (FMF) was ruled out because the patient had no skin lesions nor did she meet the age criteria for onset of the disease. Antinuclear Antibodies (ANA) and anti-DNA were discovered, and 24-hour urine was collected to rule out connective type Systemic Lupus Erythematosus (SLE). Pulse corticosteroids were initiated for 3 days, showing gradual improvement. ANA were observed in 1/160, which were considered insignificant taking into account the personal history of hypothyroidism. Anti-DNA antibodies were negative and proteinuria levels were detected <1 gram in 24-hour urine. She was discharged because ADR was considered as resolved. The patient was asymptomatic without dyspnea or respiratory distress. She had a normal blood count and HCV RNA undetectable (<15 IU / ml), continuing home treatment (manidipine and irbesartan/ hydrochlorothiazide and levothyroxine) and corticosteroids in descending pattern. After the first assessment by the Department of Gastroenterology, a month after discharge, normal liver function was observed: GPT 17.9 U / L ; GOT 28 U / L and total bilirubin 0.50 mg / dL., continuing with undetectable HCV RNA (<15 IU / ml).

Discussion

Poliserositis is an inflammation affecting several serous membranes. The most frequent symptoms are tachycardia, abdominal distention, chest pain, fever, etc, and it can be manifested as recurrent pericarditis or pleural effusion, among other disorders. Some inflammatory diseases of genetic origin, such as FMF are characterized by recurrent and brief episodes of fever, inflammation of the lining of the abdominal and thoracic cavity, inflammation and joint pain, as well as skin lesions [4]. Also, in the case of patients with SLE, affectation of serous membranes, especially of the pleura and the pericardium can be seen during the course of the disease [5]. In our case, both diseases were ruled out as alternative causes. A literature search for this clinical picture was conducted by the Pharmacy Service in different biomedical databases (BIOSIS Previews®, Current Contents® Search, EMBASE®, EMCare®, MEDLINE®, SciSearch®), to determine possible interactions concerning home treatment. No published literature on similar cases and no clinically relevant interaction with concomitant treatment were found. There have been cases of hepatic decompensation and liver failure during treatment with ombitasvir / paritaprevir / ritonavir in combination with dasabuvir with or without ribavirin, being contraindicated the use of this combination in patients with severe hepatic impairment (Child-Pugh C). Laboratory abnormalities were also observed by detecting elevated serum GPT levels (treatment had to be stopped in some instances), as well as, elevated serum bilirubin levels (in this case, no patient had to discontinue the treatment) [1,2]. This adverse effect was reported to the Spanish Pharmacovigilance System (SEFV). We also consulted related adverse reaction reports and found that two similar cases had been reported [6]. To assess the possible relationship of poliserositis to the administration of antiviral treatment, the modified Karch Lasagna [7] algorithm was applied. A score of 6 was obtained, concluding an adverse effect as "Probable". The ADR was consistent over time with drug administration, improving with drug withdrawal. Treatment was not re-administered because the HCV RNA remained unchanged (<15 IU / ml) in all the analytical tests. SVR was achieved after only 2 weeks of antiviral treatment.

Conclusion

Our patient presented a picture of poliserositis related to the administration of antiviral treatment, which required hospitalization in the ICU. We consider it very important to report suspicions of this kind, especially when this medication is used for serious disorders, and when the safety profile is not well known.

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