CASE REPORT

Efficacy and safety of Glecaprevir/Pibrentasvir in the treatment of mixed cryoglobulinemia due to chronic hepatitis C cirrhosis in a patient with chronic kidney disease

Papadopoulos N, Flouda S, Sveroni E, Tatarida Palla M C, German V

1st Department of Internal Medicine, 417 Army Share Fund Hospital of Athens, Greece

Abstract

Background: Currently, direct-acting antivirals (DAAs) are the first-line treatment for patients with chronic hepatitis C (CHC) and mixed cryoglobulinemia syndrome (MCS). However, the prognosis is variable as the achievement of sustained virological response (SVR) is not always associated with clinical remission of MCS.

Case Report: We describe a case of CHC-MCS treated with the new DAA combination Glecaprevir/Pibrentasvir (GLE/PIB). The reported patient achieved SVR accompanying by complete clinical remission of MCS.

Conclusion: Patients with CHC-MCS vasculitis would benefit from antiviral treatment with GLE/PIB. HIPPOKRATIA 2019, 23(1): 30-32.

Keywords: Chronic hepatitis C, mixed cryoglobulinemia syndrome, direct-acting antivirals, Glecaprevir, Pibrentasvir

Corresponding author: Nikolaos Papadopoulos, 10-12 Monis Petraki, 11521, Athens, Greece, tel: +306932604019, fax: +302117100671, e-mail: nipapmed@gmail.com

Introduction

Chronic hepatitis C (CHC) represents a global healthcare problem, with approximately 71 million people chronically infected[1]. Circulating mixed cryoglobulins are detected in 40-60 % of CHC patients, leading to a major extrahepatic complication called as mixed cryoglobulinemia syndrome (MCS). MCS is characterized by polyclonal immunoglobulin G and monoclonal (type 2) or polyclonal (type 3) immunoglobulin M with rheumatoid factor activity production[2]. The clinical manifestations of CHC-MCS result from small to medium vessel vasculitis and include palpable purpura, arthritis, hepatosplenomegaly, peripheral neuropathy, glomerulonephritis, and central nervous system involvement[3]. Treatment of CHC-MCS vasculitis remains difficult and should target the downstream B cell arm of autoimmunity and the viral trigger to obtain a clinical resolution of symptoms[4]. The use of new interferon-free, direct-acting antivirals (DAA's), regimens seems ideal in this setting of patients and is now recommended by the European Association for the Study of the Liver (EASL) 2018 guidelines[5]. However, there is not much experience from treating CHC-MCS patients with DAAs, since major studies did not include adequate numbers of patients with extrahepatic manifestations of CHC. Glecaprevir/Pibrentasvir (GLE/PIB) is a fixed-dose combination regimen of a new generation NS3/4A and NS5A inhibitor with potent antiviral activity against all HCV genotypes[5]. We report a 68-year-old man with CHC genotype 2 and MCS vasculitis who has been successfully treated with GLE/PIB and had achieved sustained virological response (SVR) 12 weeks after the end of treatment (SVR12).

Case Report

A 68-year-old white male with a history of atrial fibrillation, chronic kidney disease due to arterial hypertension, and hypothyroidism was admitted to our hospital because of fatigue, fever of 38°C and rash of the buttocks and lower legs. Physical examination revealed palpable purpura of the trunk and the lower extremities. A chest X-ray and electrocardiogram revealed no abnormalities. Initial complete blood cell count and biochemical tests revealed: anemia (hemoglobin: 11.9 g/dL, hematocrit: 33.4 %), leukocytosis (white blood cell count: 12.6 × 10^3/μL with neutrophils 79 %, lymphocytes 11 %, monocytes 6 %, and eosinophils 3 %), aspartate aminotransferase (AST) 50 [normal range (NR): 9-36] U/L, alanine aminotransferase (ALT) 67 (NR: 10-28) U/L, γ-glutamyltransferase (γ-GT) 43 (NR: 9-30) U/L, total bilirubin 1.2 (NR: 0.2-1.2) mg/dL, direct bilirubin 0.8 (NR: 0-0.3) mg/dL, and C-reactive protein 33.1 (NR: 0-5) mg/dL. The estimated glomerular filtration rate (eGFR) was 24 mL/min, according to the MDRD formula (Table 1). An abdominal ultrasound revealed no abnormalities.

Further laboratory testing was positive for rheumatoid factor (RF) with concomitant low levels of C3: 60 (NR: 90-180) mg/dL, and C4: 7 (NR: 10-40) mg/dL. Cryoglobulins were positive, while serum protein electrophoresis and immunoelectrophoresis did not reveal

Table 1: Laboratory evaluation of the reported patient with chronic hepatitis C and mixed cryoglobulinemia syndrome, treated with the new direct-acting antiviral combination, prior and after sustained virological response (SVR) achievement.

	Initial	SVR12	Nine months after SVR12
Hct (%)	33.4	41.6	41
Urea (mg/dl)	91	73	50
Creatinine (mg/dl)	2.5	1.5	1.1
Creatinine clearance (MDRD) (ml/min)	24	43	61
AST (U/L)	50	18	20
ALT (U/L)	67	16	22
Alkaline phosphatase (U/L)	126	63	55
γGT (U/L)	43	16	18
Cryoglobulins	Positive	Negative	Negative
LSM (kPa)	14	8.5	8.2

SVR: Sustained Virological Response, Hct: Hematocrit, MDRD: Modification of Diet in Renal Disease, AST: Aspartase Aminotransferase, ALT: Alanine Aminotransferase, γ-GT: γ-Glutamyltransferase, LSM: Liver Stifness Measurement.

monoclonal immunoglobulin. These findings were compatible with type III mixed polyclonal. Testing for anti-HIV1/2, HBsAg, anti-HBs, anti-HBc, anti-HAV were all negative while anti-HCV was positive using commercially available assays. Serum HCV-RNA was detected as 0.1 x 10^5 IU/ml (Cobas Ampli Prep/Cobas Taq Man HCV Test) and has been genotyped as 2a/2c (INNO-LIPA HCV II). Liver stiffness measurement (LSM) was performed using transient elastography (TE), raising a value of 14 kPa, which was compatible with liver cirrhosis (F4)[5]. A diagnosis of CHC and cryoglobulinemia vasculitis was established. The patient's first assessment with the Birmingham Vasculitis Activity Score (BVAS) revealed a score of 14. Due to his renal impairment, we decided to treat him with sofosbuvir free DAA combination. Thus, he received GLE/PIB 100mg/40mg three tablets orally once daily for 12 weeks, according to EASL guidelines as a treatment naïve cirrhotic patient[5].

The patient has been followed-up for 12 months: no side effect was observed during or post-treatment. Eventually, he achieved an SVR12 accompanied by complete clinical remission of vasculitis, while the BVAS re-assessment score was 0. Furthermore, he achieved laboratory clearance of cryoglobulins while his renal function significantly improved (eGFR: 43 ml/min). Thus, our patient achieved complete clinical and laboratory remission of MCS only by antiviral treatment without additional immunosuppressive therapy. Moreover, liver stiffness re-evaluation has been estimated to be 8.5 kPa, which was compatible with advanced fibrosis (F3), indicating liver fibrosis improvement. In the next nine months after SVR12 achievement, renal function showed further improvement with an estimated eGFR of 61 ml/min and no clinical or laboratory indications of MCS (complete clinical and laboratory response). The liver fibrosis stage has been stabilized to F3 (Table 1).

Discussion

CHC-MCS vasculitis is a severe and challenging condition with up to 40 % of death in ten years and overall risk of non-Hodgkin's lymphoma 35 times higher than in the general population[6]. Serologically, CHC-MCS is characterized by circulating cryoglobulins, hypocomplementemia, and a positive rheumatoid factor. CHC-MC vasculitis can be severe and life-threatening, with an estimated 5-year survival rate of 75 %[6]. Moreover, the presence of circulating cryoglobulins may be an independent risk factor for nonresponse to antiviral treatment with interferon-based regimens. It has been hypothesized that high levels of inflammatory chemokines or the use of immunosuppression in patients with CHC-MCS have predisposed them to nonresponse to interferon-based therapies that relied on host immune response[4]. Since late 2013, several novel DAAs have been approved for HCV treatment. These regimens are highly effective with an excellent SVR rate of >90 % and well-tolerated with few side effects[7]. Although prognosis is variable as the achievement of SVR is not always associated with clinical remission of CHC-MCS, the available data indicate that treatment with DAAs improves extrahepatic manifestations in most of the patients[4,8,9]. Sofosbuvir (SOF) inhibits the hepatitis C NS5B protein and has a pangenotypic antiviral effect. SOF is considered a back-bone regimen in the treatment of CHC due to its high barrier resistance. However, approximately 80 % of SOF is renally excreted, and its safety has been questioned in patients with severe renal impairment (eGFR <30 ml/min)[5]. New generation DAAs, including GLE/PIB, offer the opportunity of a shorter course of therapy (8 weeks) for selected patients regardless of genotype with an excellent safety profile and no significant drug interactions[10]. Moreover, the EXPEDITION-4 trial conducted on patients with stage 4 or 5 chronic kidney disease (CKD) treated with the fixed-dose combination of GLE/PIB for 12 weeks, with an overall SVR of 98 % and no serious adverse events[10]. To our knowledge, this is the first report to suggest the use of GLE/PIB in CHC-MCS.

Conflict of interest

Authors declare no conflict of interest

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