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CASE REPORT

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SVR 24 Achievement Two Weeks After a Tripled Dose of Daclatasvir in an HCV Genotype 3 Patient

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ABSTRACT

Directly-acting antivirals (DAA) have changed the chronic hepatitis C virus (HCV) infection therapeutic scenario allowing virus eradication in more than 95% of patients, independently from the genotype, with 12 to 24-week treatment regimens. We describe a 51-year-old Pakistani man with a chronic HCV-genotype 3 (GT3a) infection with moderate liver fibrosis, who achieved sustained virological response (SVR) 24 after a tripled dose of Daclatasvir (DCV) taken erroneously associated to Sofosbuvir (SOF). The patient had a concomitant intestinal TB infection whose treatment had been delayed in order to firstly eradicate HCV to reduce the liver toxicity of anti-mycobacterial drugs. Thanks to the cultural mediator support, we explained to the patient the correct posology of each drug to take during the day consisting of 12 week SOF (400 mg daily) plus DCV (60 mg daily) regimen. He returned 13 days after for a programmed visit and we were surprised to learn that he had taken 3 pills of DCV (180 mg/daily) instead of one, thus ending DCV assumption after only 9 days while SOF was taken correctly. He complained no symptoms. We immediately performed blood test that showed alteration of lactate dehydrogenase, creatine phosphokinase, and creatin kinase MB activity. At day 15 we stopped SOF closely monitoring the patient. Blood test alterations returned normal after one week of treatment suspension, HCV viremia remained suppressed after 4, 12 and 24 weeks proving HCV eradication. If confirmed, these data could suggest that higher doses of DCV, if tolerated, might be employed in short-time HCV-GT3 treatment.

Key words. Chronic HCV infection. HCV-genotype 3. Directly-acting antivirals. Daclatasvir. HCV eradication.

INTRODUCTION

Directly-acting antivirals (DAA) have radically changed the chronic hepatitis C virus (HCV) therapeutic scenario, as treatment options with excellent efficacy, safety profiles and, shorter treatment, are now available for most patients.

Currently, treatment regimens are still largely dependent on HCV genotype and stage of liver disease, with duration ranging between 12 and 24 weeks.[1,2]

In Italy, genotype 1 predominates (in particular 1b), which is found in about 50% of infected people. Genotypes 2, 3 and 4, which are most common in geographic areas where prevalence of infection is high (Asian countries, Eastern Europe and Egypt) show an increasing frequency in Italy due to migration flows.[3] HCV genotype 3 (GT3) infection remains one of the most challenging of all of the commonly encountered genotypes in the United States and in Europe (Western Europe), Italy included.[4]

The best DAA combinations for GT3 HCV treatment in non-cirrhotic patients are Sofosbuvir (SOF)/Velpatasvir (VEL) and SOF plus Daclatasvir (DCV), the latter currently available in Italy since 2015, which can achieve sustained virological response (SVR) after 12 weeks in 98-97% of patients, respectively.[5]

We describe a non-cirrhotic patient who achieved SVR at post-treatment week 12 and 24 after erroneous dose assumption of Daclatasvir (DCV) associated to Sofosbuvir (SOF) therapy for chronic HCV-GT3 infection.

CASE REPORT

In June 2015, a 51-year-old Pakistani man came to the Infectious Disease Unit of the University of Ferrara for positive Quantiferon (Quantiferon TB Gold®) test with normal chest radiography. In 1993, the patient had been hospitalized in a Pakistani hospital for nodal tuberculosis

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(TB) and was treated for 6 months but was unable to remember the drugs he took. Although he had been in Italy since 2012, he could neither speak nor understand Italian; consequently, a cultural mediator was needed for the medical interview and examination. His past history revealed nothing remarkable except a 5 kg weight loss in the last four months. He did not complain of any symptoms. This notwithstanding, further evaluations showed aspartate aminotransferase transaminases (AST) of 104 U/L (normal range 1-50 U/L), alanine aminotransferase (ALT) of 154 U/L (normal range 1-50 U/L) and bilirubin of 1.39 mg/dL (normal range, 0.1-0.3 mg/dL). Anti-HCV test was positive and viral load at the time of first visit was 0.162 x 106 IU/mL (real-time HCV; Cobas AmpliPrep/Cobas TaqMan HCV test [Roche Roche Diagnostics, Meylan, France] (detection limit 15 IU/mL). A chronic HCV infection was thus proved without evidence of known risk factors for HCV. HIV and HBV tests resulted negative. He underwent several instrumental and laboratory investigations to evaluate if the liver disease was caused by HCV alone or if whether there was a concomitant extrapulmonary tubercular infection. Abdominal ultrasound, chest and abdominal CT scan as well as colonoscopy with biopsy, gastroscopy and liver biopsy were done carried out. The above investigations allowed us to rule out a liver involvement as possible extrapulmonary manifestation of TB. Conversely, colon biopsy showed lymphoplasmacytic and eosinophilic inflammatory infiltration and epithelioid granulomas. The mycobacterium culture performed on a portion of colon tissue resulted positive for *M. tuberculosis* which was susceptible to first-line drug therapy. Therefore, given the need to start an anti-TB treatment, we decided, firstly, to establish the stage of liver disease. Fibroscan was not feasible due to the patient's body size (BMI 32), so he underwent to a liver biopsy which showed moderate fibrosis (Ishak score: 9; Metavir score: 3). In order to reduce liver toxicity before initiating anti-TB therapy, we decided to apply the following procedure: antiviral therapy with DAA to obtain an improvement in liver function and then, anti-TB therapy. At the beginning of therapy (July 2016), the patient showed an impaired liver function with AST level of 267 IU/L (normal range 1-50 U/L), alanine aminotransferase (ALT) of 238 IU/L (normal range, 1-50 U/L) and slight elevation in serum bilirubin values of 1.37 mg/dL (normal range, 0.1-0.3 mg/dL). Abdominal ultrasound and gastroscopy ruled out any sign of hepatic cirrhosis. Viral load of HCV-RNA was low, equal to 0.0301 x 106 IU/mL (detection limit 15 IU/mL) and the patient's HCV genotype was found to be GT3a. Thus, we started therapy with SOF (Sovaldi®, Gilead Sciences) 400 mg daily plus DCV (Daklinza®, Bristol-Meyers Squibb) 60 mg daily. We explained to the patient, thanks to the cultural mediator support, the correct posology of each drug to take during the day. However, when he returned to our Institution after 13 days for a programmed visit, we were surprised to learn that he had taken three pills of DCV daily instead of one, thus ending DCV assumption after only 9 days and had taken SOF only for the remaining 6 days. Although the patient did not complain of any symptoms, we immediately performed blood tests and an electrocardiogram to check whether the patient presented alterations due to the DCV overdose. Some laboratory examinations including Lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and creatin kinase MB activity (CK-MB) resulted abnormally increased (348 U/L [normal range, 0-248 U/l], 479 UI/l [normal range, 0-170 U/L] and 15.8 UI/L [normal range, 0-5 ng/mL, respectively), so that antiviral therapy was stopped. These parameters returned to normal values one week after suspension of antiviral therapy and the patient never complained of any symptoms. No alterations in haematological parameters were observed. Overall, the patient assumed DCV 60 mg 3 times daily for 9 days and SOF 400 mg for 15 days. He did not assume any other treatment for HCV infection, or for intestinal TB. Transaminases values and HCV RNA were checked at 4, 12 and 24 weeks after treatment suspension. We witnessed the persistent normalization of AST and ALT values, and HCV-RNA was undetectable after 12 and 24 weeks from termination of treatment.

DISCUSSION

HCV-GT3 is common worldwide, accounting for around 30% of infected patients in Northern Europe and Asia. Compared with other genotypes, GT3-infection, which is highly prevalent in South East Asia and in drug users, has been associated with an increased risk of the progression of fibrosis, steatosis and the development of hepatocellular carcinoma in patients with cirrhosis.[6]

Historically, treatment of HCV-GT3 infected patients included pegylated interferon (Peg-IFN) alpha 2a or 2b plus ribavirin for 16 to 48 or 72 weeks based on response.[7] Although this combination was previously the standard of care, it is currently not recommended by either European or American treatment guidelines because of low SVR rates and poor tolerability.[8] Currently, this regimen has largely been replaced with DAAs which, by targeting non-structural (NS) viral proteins, have markedly improved the prognosis of HCV infection and HCV-GT3, a highly prevalent infection worldwide. Three DAAs are approved by the Food and Drug Administration and European Medicines Agency, for the treatment of HCV-GT3 with an all-oral regimen: SOF, a pan-genotypic nucleotide analog inhibitor of HCV NS5B polymerase; VEL, a next-generation pan-genotyp-

Table 1. Major articles regarding HCV short duration therapy (less than12 weeks).

Author (publication year)	Genotype (Patients, n)	DAA combination	Duration (weeks)	Outcome (SVR 12/treated)
Wyles, DL (2015)	1 (41) 2 (6) 3 (3)	Daclatasvir plus Sofosbuvir	8	GT1: 31/41 GT2: 5/6 GT3: 2/3
Sulkowski, MS (2017)	1 (28)	Daclatasvir/ Asunaprevir/ Beclabuvir plus Sofosbuvir	4/6	4 week regimen: 4/14 6 week regimen: 8/14
Lawitz, E (2017)	1 (102) 3 (41)	Elbasvir/ Grazoprevir plus Sofosbuvir	4/6/8/12	GT1 without cirrhosis 4 week regimen: 10/31 GT1 without cirrhosis 6 week regimen: 26/30 GT1 with cirrhosis 6 week regimen: 16/20 GT1 with cirrhosis 8 week regimen: 17/21 GT3 without cirrhosis 8 week regimen: 14/15 GT3 without cirrhosis 12 week regimen: 14/14 GT3 with cirrhosis 12 week regimen: 10/12

ic NS5A inhibitor and DCV, a pan-genotypic inhibitor of HCV NS5A metalloprotein[1,7] which has picomolar activity against wild-type HCV-GT3, and a pharmacokinetic profile that allows once-daily dosing.

In phase III of the ALLY-3 study, the SVR rate at post-treatment week 12 (SVR12) with DAA was shown to be 96% in HCV-GT3-infected patients without cirrhosis, regardless of past HCV treatment experience, with good tolerability.[5,9] Moreover, for patients without cirrhosis, RBV-free treatment with DCV-SOF for 12 weeks is highly effective for treatment for HCV-GT3.[10]

To our knowledge, this is the first described case of SVR 12 and 24 following a short course of antiviral treatment with DAAs in an HCV-GT3 patient.

Over the last decade, various INF-based therapeutic regimens have been experienced in HCV infected patients with different genotypes which led to the achievement of high rates of SVR after 12 weeks of therapy.[11] Recently, a case of a cirrhotic woman with chronic HCV and HIV co-infection who reached SVR after an ultra-short course (10 days) of triple therapy with antiviral treatment, was reported.[12]

Our patient had erroneously taken a tripled dose of DCV (180 mg/day) without complaining of any symptoms, although there were biochemical impairments in his blood test examinations. These, however, did not produce any clinical manifestations and became reversible soon after drug discontinuation.

The described case is clinically relevant because of the patient's peculiar but positive clinical outcome. We hypothesized a very fast clearance of HCV viremia because of the higher DCV load assumption. The achievement of SVR-24 was not expected at all after only 15 days of DAA assumption. As shown in table 1, a consistent number of reports concern short duration therapy of HCV-GT1 infection,[13,10,14] whereas very few data exist in regarding HCV-GT3 infected patients. Recent data support the use of 8-12 week treatment regimens with other DAA regimens that maintain high efficacy for patients with HCV-GT3 infection with or without cirrhosis.[10]

In contrast with the previous INF-based regimens,[15] no correlation has been found so far between the viral load at baseline and a favorable outcome with the latest DAAs, except for the Elbasvir- Grazoprevir combination.[2] Despite this lack of evidence, we can speculate that the low viral load detected at baseline in our patient, could have contributed to clear HCV rfaster. In fact, the beneficial result achieved with an erroneous three-fold increase in DCV doses caused a quick and complete HCV suppression and negligible blood biochemical changes except for the fleeting rise of in LDH, CPK, and CK-MB, which promptly became normal.

If confirmed on a large number of cases, these data could serve to investigate whether higher doses of DCV, if tolerated, could be employed to reduce the time and cost of this treatment for HCV-GT3 infection.

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CONFLICT OF INTEREST

No potential competing interests to declare.

ABBREVIATIONS

- **ALT:** alanine aminotransferase.
- **AST:** aspartate aminotransferase.
- **CK-MB:** creatin kinase MB activity.
- **CPK:** creatine phosphokinase.
- **DAA:** directly-acting antivirals.
- **DCV:** daclatasvir.
- **LDH:** lactate dehydrogenase.
- **SOF:** sofosbuvir.
- **TB:** tuberculosis.
- **VEL:** velpatasvir.

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