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

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INTRODUCTION

Directly-acting antivirals (DAA) have radically changed the chronic hepatitis C virus (HCV) 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.
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-
ic NS5A inhibitor and DCV, a pan-genotypic inhibitor of HCV NS5A metalloprotein, 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. Moreover, for patients without cirrhosis, RBV-free treatment with DCV-SOF for 12 weeks is highly effective for treatment for HCV-GT3.

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.

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. As shown in table 1, a consistent number of reports concern short duration therapy of HCV-GT1 infection, 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.

In contrast with the previous INF-based regimens, 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. 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 faster. 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.

Table 1. Major articles regarding HCV short duration therapy (less than 12 weeks).

<table>
<thead>
<tr>
<th>Author (publication year)</th>
<th>Genotype (Patients, n)</th>
<th>DAA combination</th>
<th>Duration (weeks)</th>
<th>Outcome (SVR 12/treated)</th>
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<tr>
<td></td>
<td>2 (6)</td>
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<td>3 (3)</td>
<td></td>
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<tr>
<td>Sulkowski, MS (2017)</td>
<td>1 (28)</td>
<td>Daclatasvir/ Asunaprevir/ Beclabuvir plus Sofosbuvir</td>
<td>4/6</td>
<td>4 week regimen: 4/14 6 week regimen: 8/14</td>
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<tr>
<td>Lawitz, E (2017)</td>
<td>1 (102)</td>
<td>Elbasvir/ Grazoprevir plus Sofosbuvir</td>
<td>4/6/8/12</td>
<td>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</td>
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<td>3 (41)</td>
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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.

REFERENCES


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