

Glecaprevir/pibrentasvir ultra-short treatment to cure HCV infection: case report and literature review

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SUMMARY

Shortening therapy duration with direct-acting antiviral agents (DAAs) is desirable to pursue the WHO target of HCV eradication by 2030. We report two cases of HCV-infected women who achieved sustained virologic response after an ultra-short treatment with glecaprevir/pibrentasvir (G/P), discontinued due to cutaneous adverse events, and analyze similar cases reported in the literature. Female gender seems to be a

prevailing characteristic in this group of patients. G/P, due to its pangenotypic and strong antiviral activity, may represent a candidate for a shortened DAA regimen in non-cirrhotic treatment-naïve subjects.

Keywords: Chronic hepatitis C, glecaprevir/pibrentasvir, ultra-short treatment, gender, cutaneous adverse events.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection represents a world-wide health problem leading to cirrhosis, its complications and increased mortality. Successful treatment of HCV reduces disease progression and transmission [1]. According to current guidelines the duration of antiviral therapy with direct-acting antiviral agents (DAAs) in patients without cirrhosis ranges from 8 to 12 weeks, depending on genotype [2]. Several studies aimed to reduce treatment duration to less than 8 weeks. Overall, the sustained virologic response (SVR) rate after 6-weeks of a combination treatment including 3 or 4 DAAs resulted lower than that observed in patients treated with 8 or 12-weeks regimens. However, low baseline vi-

ral load (VL), young age and genotype-1b were identified as predictors of response to a shortened treatment [3]. In this regard, glecaprevir/pibrentasvir (G/P) represents a novel, second generation, pangenotypic regimen with excellent characteristics of efficacy and tolerability [4, 5]. In a pilot study conducted among people with recent HCV infection, a 6-weeks regimen of G/P was highly effective (SVR rate 96%) and safe [6]. Moreover, a recent retrospective viral kinetic analysis demonstrated that a modelling-based, response-guided approach predicted a cure time with G/P <8 weeks in 67% of treatment-naïve cirrhotic patients and <7 weeks in 64% of the overall population (cirrhotic and non-cirrhotic subjects) [7].

Herein, we report two cases of HCV infected women who achieved SVR after an ultra-short treatment course with G/P, discontinued due to cutaneous adverse events. Both patients provided informed consent to data publication.

Furthermore, we performed a literature investigation using PubMed search engine (<https://>

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pubmed.ncbi.nlm.nih.gov/) to identify prior reports of HCV eradication after ultra-short DAAs non-standard therapy.

■ CASE REPORTS

Patient 1. A 42-year-old woman affected by chronic hepatitis C (CHC) presented to the Hepatology Unit of Policlinico Umberto I Hospital in Rome, Italy. The diagnosis went back 15 years, but she was treatment-naïve. Clinical history included childhood bronchial asthma and seasonal pollen allergy. Blood count, liver and kidney function tests were normal, HCV genotype was 3a, and basal viral load was 7.1×10^5 IU/mL. Abdomen ultrasound showed mild hepatomegaly, and liver stiffness (*Fibroscan*) was 5.0 kPa, corresponding to fibrosis stage 0-1 [8]. She did not report concomitant medications or previous drug-related adverse events (AEs). An 8-weeks G/P treatment was prescribed. On the eighth day of administration an intense local itching appeared on her right arm. She arbitrarily discontinued G/P and, two days later, showed up at the outpatient clinic referring the matter. The patient was in good general conditions and physical examination was negative. New liver function, blood count and coagulation tests were normal. Rupatadine 10 mg was prescribed for pruritus that regressed over the next seven days. HCV-RNA resulted undetectable by Roche Taqman real-time PCR (lower limit of quantification (LLQ) 15 IU/ml) at one, three and twelve months after the end of treatment (EOT).

Patient 2. A 78-year-old woman affected by CHC presented to the Hepatology Unit of Policlinico Umberto I Hospital in Rome, Italy. Clinical history included stage-3a chronic kidney disease according to KDIGO (e-GFR 53 mL/min/1.73 m²) and subclinical hypothyroidism. She reported non-steroid-anti-inflammatory drugs hypersensitivity. HCV infection had been diagnosed one year before. Blood count and liver function tests were normal, HCV genotype was 1b, basal viral load was 1.1×10^5 IU/mL. Abdomen ultrasound was unremarkable and liver stiffness was 4.1 kPa (fibrosis stage 0-1) [8]. G/P was started with an expected duration of 8 weeks. The only concomitant medication was Psyllium-based laxative. After two days of administration, an intense

itching appeared on her arms, abdomen, and head without rash. She was prescribed cetirizine 10 mg/day and continued antiviral therapy. The fourth day severe itching persisted, with nighttime worsening and difficulty in sleeping. On physical examination there were no respiratory distress, skin rash or jaundice. Betamethasone 2 mg/day was added to treatment. The fifth day the itching worsened, with extension to ocular region and onset of nausea: G/P was discontinued. Blood exams remained normal, except for a slight increase of bilirubin (total 1.69 mg/dL, direct 0.72 mg/dL), that normalized a week later. Cetirizine and betamethasone continued for further five days, until resolution of itching. HCV-RNA resulted undetectable by Roche Taqman real-time PCR (LLQ 15 IU/ml) at one, six and twelve months after EOT.

■ DISCUSSION

Current guidelines recommend 8-weeks G/P treatment in CHC non-cirrhotic treatment-naïve [1]. This regimen is safe and well-tolerated, with a discontinuation rate of 0.5-2%; on the upside, pruritus is the most common AE, occurring in 2.5-14.7% [4, 5]. Our patients experienced a localized not-debilitating pruritus (grade 1 according to Common Terminology Criteria for Adverse Events version-5.0, CTCAE-5) in the first case and a widespread pruritus limiting sleep and necessitating of oral corticosteroid (grade 3 according to CTCAE-5) [9] in the second one. These cutaneous AEs caused an early treatment discontinuation, after 8 and 5 days, respectively. Considering the HCV-RNA undetectability one-month after treatment discontinuation, we decided not to begin a new therapy with other anti-HCV drugs but to continue follow-up. Despite the extreme shortness of antiviral treatment, the patients achieved and maintained SVR.

G/P is a pangenotypic DAAs regimen with a strong antiviral potency and a high barrier to resistance. Surprisingly, compliance is currently not considered a limiting factor for SVR when treated with G/P, so that this combination was defined a “forgiving regimen” in patients treated with G/P [10]. DAAs, which inhibit critical steps in the HCV replication cycle, induce not only hepatocyte elimination, but also a progressive reduction of intracellular viral content down to

its disappearance (cell cure), leading to SVR [11]. In fact, a recent *in vitro* study demonstrated that a triple DAAs combination induces virological cell cure after 15 days of exposure, but 6 and 9 days of treatment were associated with virological relapse and development of resistance mutations [12]. Therefore, other factors may have contributed. Interestingly, Li and colleagues also demonstrated that relapse was avoided with an increased DAAs dosage, even with an intermittent regimen, mimicking the phenomenon of low compliance [12]. Thus, a possible explanation of why our patients achieved an SVR with an ultra-short therapy is that they underwent to a pharmacological overdose that was concurrently responsible for the dermatological AEs. Unfortunately, drug monitoring for G/P serum concentrations was not available.

A limited number of reports describing successful treatment with DAAs lasting less than 4-weeks has been retrieved in the literature and the main characteristics are briefly summarized in Table 1. The median-IQR age at the time of treatment was 56 years (30), the median-IQR baseline VL was 6.5×10^5 UI/mL (11.9) and 5 out of 9 patients (56%) were cirrhotic. Genotype-1b was the most prevalent (56%) and ombitasvir/paritaprevir/ritonavir/dasabuvir+ribavirin was the most prescribed regimen (44%). Ethnicity (not reported) was available in only 5 patients, 4 of them (80%) Caucasian. Intriguingly, the factor that better characterizes this small group is gender, as 8 out of 9 subjects (89%) were females.

This observation tallies with the known gender-related immunological differences, whereby women have a more potent cytotoxic immunity and obtain more frequently viral clearance, both spontaneous and treatment-induced, compared to men. Furthermore, it has been demonstrated that CHC implies a degree of virus-induced immunosuppression, while the administration of DAAs restore HCV specific CD8⁺ T-cells and reconstitute CD4⁺ compartments [13]. Therefore, it is possible that, after an initial phase of rapid viral decline produced by G/P, consistent with the conventional biphasic model of viral clearance, the immune system completed the eradication of HCV, even in the absence of a pharmacological support [7].

In the pre-DAAs era, cutaneous AEs, such as pruritus and/or rash, were common during treatment with PEG-IFN+RBV; subsequently, with the introduction of first generation DAA protease-inhibitor telaprevir (TPV), almost 50% of patients reported rash/pruritus. Although the implication of pyrazinoid acid, a major metabolite of telaprevir, was proposed, the pathogenesis of DAAs-associated cutaneous AEs is still unclear [14]. To date, the main hypothesis considers the central role of the integumentary system both in immunity and in the metabolism of xenobiotics and postulates a T-cell-dependent immune-mediated mechanism triggered by a bioactivated reactive metabolite and facilitated by the systemic immune-activation state, typical of chronic viral infections [15]. In our cases, the de-

Table 1 - Cases of ultra-short treatment.

Reference	Regimen	Age	Gender (M/F)	Cirrhosis	Genotype	Baseline viral load ^a	Days of treatment
Zampino, 2018 [16]	OPrD+RBV	61	M	✓	1b	7,0	28
Zampino, 2018 [16]	OPrD+RBV	56	F	✓	1a	18,0	28
Meissner, 2014 [17]	SOF+RBV	50	F		1a	0,12	27
Huang et al., 2016 [18]	OPrD+RBV	81	F		1b	0,17	25
Hasin et al., 2016 [19]	OPrD+RBV	74	F	✓	1b	20,0	24
Sato et al, 2016 [20]	DCV+ASV	55	F	✓	1b	6,5	17
Hasson, 2014b [21]	TPV+PEG-IFN+RBV	40	F	✓	1c	3,6	10
Present report, case 1	G/P	42	F		3a	7,1	8
Present report, case 2	G/P	78	F		1b	1,1	5

^aHCV-RNA x 105 IU/mL; bHIV coinfecting.

Abbreviations: ASV, asunaprevir; DCV, daclatasvir; G/P, glecaprevir/pibrentasvir; OPrD, ombitasvir/paritaprevir/ritonavir/dasabuvir; PEG-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TPV, telaprevir.

velopment of low to moderate grade itching was accompanied by achievement of SVR. Moreover, the type of immunity involved in DAAs-related cutaneous AE and in immune-mediated viral clearance are similar. Therefore, it is our opinion that the dermatological manifestations described could have represented an epiphenomenon of a systemic immunological activation, induced by the G/P-mediated rapid viral decline, which was then able to complete HCV eradication despite an ultra-short treatment course.

■ CONCLUSIONS

The identification of factors predicting high chances of SVR with an ultra-short DAAs regimen could be of great value in the global goal of HCV eradication. Female gender could represent one of these factors. Although other cases of successful ultra-short antiviral treatment have been described, these are the first reports of HCV eradication after less than ten days of treatment. We believe that further studies should elucidate if G/P combination, due its pangenotypic and strong antiviral activity, may represent a candidate for a shortened DAAs regimen in non-cirrhotic treatment-naive subjects. The possible relation between cutaneous AEs, gender-related immune system activation and rapid viral clearance still remains speculative and may deserve further investigation.

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Conflict of interest

The authors have nothing to disclose regarding conflict of interest with respect to this article.

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