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Journal of Liver and Clinical Research

Case Report

What we are Leaving Behind: …an "Ultra-Short" Triple Therapy with Telaprevir in Two Patients with Chronic Hepatitis C Genotype 1

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Submitted: 11 January 2015

Accepted: 23 February 2015

Published: 25 February 2015

Keywords

- Telaprevir
- Chronic hepatitis C genotype 1
- Anaemia, Rash
- Ultra-short treatment

Abstract

A short therapy for hepatitis C is possible considering the strategy of triple therapy with new second generation DAAs (direct antiviral agents) or interferon free therapy. While in the past telaprevir was used in triple therapy, the CONCISE study proposed an "ultra-short" therapy of 12 weeks in some categories of patients, whose aspects seem particularly advantageous for the clinician, in view of the frequent side effects of telaprevir such as anaemia and rash. In our experience, two patients reported sustained virological response, not withstanding shorter treatment.

ABBREVIATIONS

CHC: Chronic Hepatitis C Virus; SVR: Sustained Virological Response; RVR: Rapid Virological Response; Daas: Direct Antiviral Agents; Sc: Subcutaneously, Bid: Twice Daily, LSM: Liver Stiffness Measurement

INTRODUCTION

At present, the therapeutic hepatitisC background is changing because of the arrival of sofosbuvir, simeprevir, daclatasvir and the other second generation DAAs. However, up until now, we treated some of our patients suffering from chronic hepatitis C genotype 1 with pegylated interferon and ribavirin in combination with first generation protease inhibitor as telaprevir or boceprevir. In our experience, despite the complexity of management due to the large number of side effects, drug interactions, large quantities of pills taken with food [1], the triple therapy with telaprevir showed, in some categories of patients, especially naive and relapsers, to obtain SVR (sustained virological response) also with a so-called "ultra-short" duration [2]. The treatment program was 24 weeks in naives or relapsers (in absence of staging equal to F4) with eRVR (extended rapid virological response), including 12 weeks of triple therapy followed by other 12 weeks of dual therapy. While, for null responders and patients with cirrhosis (F4) (independent of previous treatment), the treatment's duration was 48 weeks (12 weeks of triple+36 weeks of dual). Considering several side effects in some patients, it was interesting to think about a short treatment limited to only 12 weeks. In fact, the CONCISE [2] study established a percentage of SVR in naive patients or non cirrhotic relapsers carrying genetic polymorphismIL28B rs12979860 C/C with eRVR, treated with 12 weeks of triple therapy, comparable to treatment in 24 weeks. It is necessary to "personalize" patient antiviral treatment. Even if the "ultra-short" triple therapy with telaprevirshouldnot be recommended; we report our experience with two naive women, treated with short duration telaprevir, because of side effects, obtaining sustained virological response.

CASE PRESENTATION 1

In 2013, a 26-year old Ukrainian woman with chronic hepatitis C (genotype 1b) (known from 2007) was examined in our Department for a clinical re-evaluation of her liver disease. She works as a shop clerk, is married and has a son in good health. She never underwent antiviral treatment due to employment problems. On August 2013, we performed a Fibro Scan with LSM (liver stiffness measurement) equal to 7.3 kPa (IQR 0.9) and an abdomen ultrasound that showed only light steatosis. Personal history was negative for alcohol, smoke, medications and risk factors for HCV infection. Baseline exams are reported in (Table 1). During medical examination, she reported to be motivated in curing her hepatitis C in virtue of a second pregnancy. Considering the positive predictive pre-treatment factors towards dual therapy (IL28B rs12979860 C/Ccarrier, naive, low fibrosis, low viral load baseline), we started lead-in as follows: Peg-IFN-α 2a 180 once weekly sc (subcutaneously) plus ribavirin

200 mg 2 c bid per os (twice daily) (patient's body weight was 57 kg) for 4 weeks. After 4 weeks, the HCV RNA was equal to 100 U/ml. Antiviral treatment was well tolerated, except for asthenia and anaemia (haemoglobinvalue11 g/dl). Although obtaining a favourable response to interferon sensitivity's test, in accordance with the patient, we added telaprevir 375 mg 3 c bid every 12 hours with fat meals. The haemoglobin value was 9.7 g/dl, only one week after taking telaprevir; so we prescribed epoietin (Eprex 40000 UI once weekly sc), without changing the dosage of ribavirin.Later, the patient reported nausea and a worsening of asthenia and she temporarily left her job. On the 4th week of triple therapy with telaprevir, HCV RNA was undetectable but the patient had erythema on the chest associated with light itching, which was resolved with steroidal topical cream (Figures 1a and 1b). After 8 weeks of telaprevir, HCV RNA was again undetectable but telaprevir therapy was ended due to a large macular popular erythema (BSA >50%) appearing in absence of fever, lymphadenopathy and/or eosinophilia (Figures 2a-2d).Two days later pegylated interferon and ribavirin therapy was interrupted. The skin lesion disappeared (Figures 3a and 3b) following use of dermatologist prescribed systemic steroidal therapy. The patient is now well and working. She was cured of her hepatitis C, obtaining SVR24 and improving liver stiffness measurement [4.6 kPa (IQR 0.9)] at the end of treatment.

Table 1: Baseline exams of the first and second patient.

	First patient (1)	Second patient (2)
WBC (10^3/mmc)	5820	5320
Hb (g/dl)	13	14.3
MCV (fL)	89	91
PLT (10^3/mmc)	254	160
AST (U/L)	21	70
ALT (U/L)	48	80
GGT (U/L)	20	68
ALP (U/L)	61	80
TOTAL BILIRUBIN (mg/dl)	0.64	0.60
DIRECT BILIRUBIN (mg/dl)	0.10	0.20
TOTAL PROTEIN (ALB, GAMMA) (g/dl)	8.0 (60%, 16%)	8.2 (55%, 23%)
INR	0.99	1.04
GLYCEMIA (mg/dl)	86	96
TOTAL CHOLESTEROL (mg/dl)	184	211
TRYGLICERIDE (mg/dl)	49	64
IL28B rs12979860 genotype	C/C	C/T
CRYOGLOBULIN/CRYOCRIT	absent	absent
αFP (ng/ml)	2.0	7.2
HCV RNA (UI/ml)	327700	1415000
CREATININ (mg/dl)	0.50	0.50
TSH (mU/L)	1.80	0.93
AMA	negative	negative
ASMA	negative	negative
aLKM	negative	negative
ANA	160 (fine speckled)	negative
ENA	negative	negative
SIDEREMIA (mcg/dl)	102	213
TRANSFERRIN (mg/dl)	257	291
FERRITIN(ng/ml)	16	185
% TRANSFERRIN SATURATION	28	51
IgG HAV (U/ml)	>100	>100
HIVAb	negative	negative
HBsAg	negative	negative
HBcAb	negative	negative
HBsAb (U/ml)	negative	>100

Abbreviations: WBC: White Blood Cell; Hb: Hemoglobin; MCV: Mean Corpuscular Volume; PLT: Platelet, AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gamma Glutamyl transpeptidase, ALP: Alkaline Phosphatase; INR: International Normalized Ratio; Alb: Albuminemia, Gamma: Gamma Globulins; TSH: Thyroid Stimulating Hormone; Ab: Antibody

CASE PRESENTATION 2

In July 2013, a 55-years old Rumanian woman was examined in our Hepatology Department for the first evidence of chronic hepatitis C (genotype 1b) with hyper transaminasemia (ALTx2 ULN). Her personal medical history included hemorrhagic gastritis caused by FANS (anti-inflammatory non steroidal

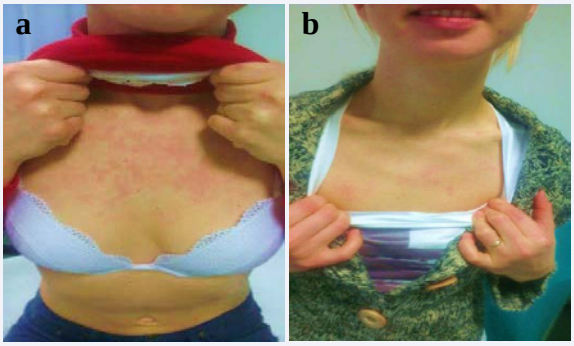

Figure 1 Light erythema (first patient).

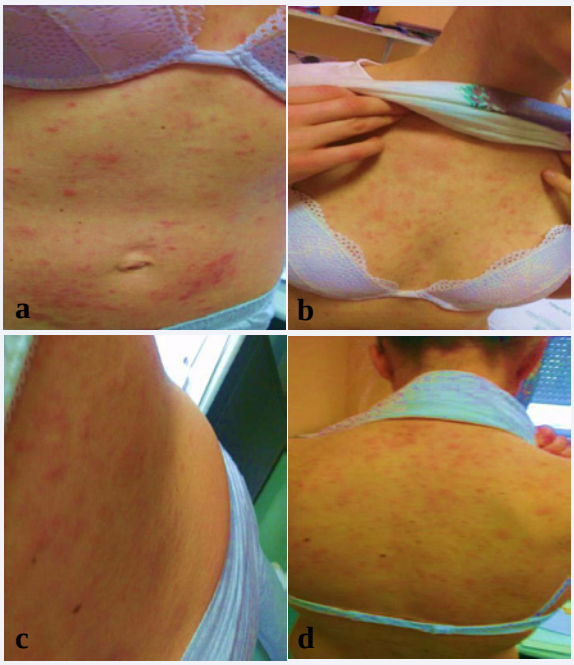

Figure 2 Large macular popular erythema on the back and on the trunk (first patient).

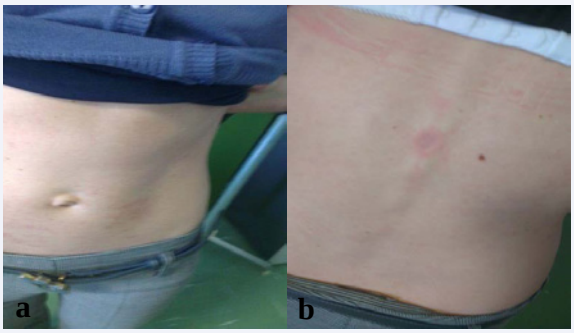

Figure 3 Disappearance of previous skin lesions (first patient).

medicines) when she was 30 years old and in that occasions he underwent a blood transfusion. She has been living in Italy since 2007 and cares for an elderly woman. Baseline exams are reported in (Table 1). We performed a Fibro Scan with LSM (liver stiffness measurement) equal to 17.5 kPa (IQR 2) and abdomen ultrasound that showed signs of chronic liver disease without splenomegaly. The EGD was negative at that time. Considering high fibrosis, we suggested triple therapy with telaprevir ab initio and the patient accepted. We started antiviral treatment as follows: Peg-IFN-α 2a 180 once weekly sc (subcutaneously) plus ribavirin 200 mg 2 c +3 c die per os (twice daily) (patient's body weight was 71 kg) plus telaprevir 375 mg 3 c bid every 12 hours with fat meals. After two weeks of triple therapy, the haemoglobin value was 10 g/dl and we prescribed epoietin (Eprex 40000 UI once weekly sc). The patient referred asthenia, nausea, rectal discomfort and after 4 weeks of triple therapy, she experienced hyperpyrexia with dyspnea and cough. We therefore prescribed amoxicillin/clavulanic acid 1 gr 1 c bid for 7 days obtaining effervescence but the cough persisted. On the 4th week HCV RNA was negative, transaminase and TSH (thyroid stimulating hormone) were normal and the uric acid value was 9.5 mg/dl. The patient later reported nausea and weight loss (about 6 kg in 8 weeks). At the 8th week, HCV RNA was undetectable but macrocytic anaemia persisted (9.4 g/dl) and at the 10th week a tooth abscess appeared requiring prolonged antibiotic therapy. The patient's standard of living worsened and again she lost weight so we reduced ribavirin dosage to 200 mg 2 c bid. At the 12th week she had lipothymia recording hypotension and she refused continuing antiviral treatment due to the worsening life quality (asthenia, dyspnoea). Considering the exams, HCV RNA was negative at the end of treatment but the haemoglobin value was8 g/dl. We took into consideration blood transfusion hoping in spontaneous recovery, after the antiviral treatment. The patient underwent blood transfusion one month after treatment because of persisting symptomatic anaemia, in absence of other causes of anaemia (for example gastroentericloss). Now the patient is well and HCV RNA is undetectable (SVR24). Liver stiffness measurement was equal to 5.6 kPa (IQR 1.0) at the end of treatment.

DISCUSSION

These two case reports underline telaprevir's efficiency using an "ultra-short" treatment (12 weeks or less), without to prejudice sustained virological response. In the first case, predictive positive pre-treatment factors were status of naive, low viral load, and genetic polymorphism IL28B rs12979860 C/C.Therefore, 4 weeks of dual therapy plus 8 weeks of triple were enough to obtain SVR, although triple therapy with telaprevir it was not recommended for use in lead-in strategy. In the second patient, even if naive, we supposed that the fibrosis was higher, while the patient experienced only 12 weeks of triple therapy, reporting SVR. However, in both cases, the presence of "similar" eRVR was the best treatment predictive factor for SVR. In conclusion, a percentage equal to 10-15% had to interrupt antiviral treatment because of severe side effects, while treatment of rash and anaemia during telaprevir use were well controlled [1]. The major problem in early interruption of treatment remains the possible absence of virological response or the induction of viral resistance. In fact, in view of our successful treatments, the "ultra-short" triple therapy should not be widely recommended and our individual successes cannot be extended on a large scale level.

ACKNOWLEDGEMENTS

The Authors are grateful to Dr. Marina Crovatto and Dr. Endri Mauro for their helpful comments and suggestions.

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Cite this article

Costa EG, Ghersetti M, Grazioli S, Casarin P (2015) What we are Leaving Behind: …an "Ultra-Short" Triple Therapy with Telaprevir in Two Patients with Chronic Hepatitis C Genotype 1. J Liver Clin Res 2(1): 1010.