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Case Report

Adverse Skin Reactions during Triple Therapy with Boceprevir in Chronic Hepatitis C Genotype 1

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- Boceprevir
- Chronic hepatitis C genotype 1
- Lead-in
- Adverse skin reaction

Abstract

Boceprevir is a first generation serin protease NS3/4A inhibitor, formally available in Italy from 2013 and often used for the treatment of CHC genotype 1, always in combination with pegylated interferon and ribavirin; known as the triple therapy. The main advantages of using boceprevir are the higher SVR percentage and shorter treatment time; 28 weeks if eRVR-extended rapid virological response is reported in some categories of patients, principally naives with intermediated stage of fibrosis, comparing to those treated with dual therapy. Then, the lead-in, a phase using only peg-interferon and ribavirin for 4 weeks prior adding boceprevir, helps the clinician to understand the utility of triple therapy in some patients who are difficult to treat, such as null responders to previous dual therapy or poor responders to interferon. Unfortunately, some side effects frequently occur during therapy with boceprevir. Apart from anaemia, dysgeusia and neutropenia, adverse skin reactions are also reported, although these dermatological side effects are less distinctive from those presented during treatment with telaprevir. So we described our case reports with cutaneous toxicity of various severity in two different types of patients - naive low fibrosis and previous null responder to the dual therapy with high fibrosis, treated with boceprevir. In fact, even if interferon free strategy and triple therapy with new second generation DAAs are becoming more prevalent, boceprevir and telaprevir with their positive and negative features represented the first step to revolutionizing the treatment of HCV-related chronic liver disease genotype 1.

ABBREVIATIONS

CHC: Chronic Hepatitis C Virus; SVR: Sustained Virological Response; RVR: Rapid Virological Response; Daas: Direct Antiviral Agents; Sc: Subcutaneously; Iv: Intravenous; Bid: Twice Daily; Tid: Three Times In A Day; LSM: Liver Stiffness Measurement

INTRODUCTION

Despite of the arrival of second generation direct antiviral agents (DAAs), until now we have treated some of our patients suffering from chronic hepatitis C genotype 1 with first generation protease inhibitors such as telaprevir and boceprevir. Certainly, the strategy of interferon free or triple therapy with simeprevir/sofosbuvir or daclatasvir will bring several advantages such as SVR high percentage, short treatment times and few side effects for all genotypes and also for "difficult" patients [1,2]. Contrarily, the triple therapy with boceprevir or telaprevir was difficult because of the many side effects, drug interactions, many pills to take and intermediated SVR, especially in patients difficult to treat, such as cirrhosis sufferers and previous null responders to dual therapy [3]. Despite these aspects, these drugs (boceprevir and telaprevir) belong to the therapeutic hepatitis C background and made history for some patients by enhancing the hepatologist's clinical experience. Particularly, considering side effects during antiviral treatment, it is well-known that it is possible to have different adverse skin reactions such as erythema in the site of pegylated interferon injections, alopecia, xerosis, itching, psoriasis and macular papular erythema. These problems can appear, according to different research papers, in about 10-15% of patients treated with dual therapy, in 50% (independently from the rash severity) with telaprevir and in 20% of those treated with boceprevir [4]. In the case of telaprevir, the SCAR (severe cutaneous adverse reaction, including Drug Reaction Eosinophliac Systemic Syndrome and Steven Johnson Syndrome) occurs in 0.5-1% of patients and because of the dermatological side effects, about a percentage equal to 5% has to stop the triple therapy, including pegylated interferon and ribavirin [4]. However, it was reported few cases of severe adverse skin reactions also for boceprevir with the interruption of the current treatment [5]. During antiviral treatment, it is difficult to distinguish between the skin side effects caused by ribavirin/pegylated interferon to those provoked by telaprevir/boceprevir but the phase of lead-

in allows the testing of a patient's "cutaneous tolerance" for the dual therapy. Finally, chronic hepatitis C is associated with extra-hepatic manifestations such as porfiria, vasculitis, lichen ruben planus, which should be assessed before beginning antiviral treatment. We report our experience of skin side effects during triple therapy with boceprevir.

CASE PRESENTATION 1

A 45-years old Ukrainian woman was admitted to our department for chronic HCV related infection (genotype 1b). The first casual detection of anti-HCV positivity dated back to 2009 on the occasion of her first pregnancy but she never experienced antiviral treatment. She underwent a blood transfusion when she was 19-years old in Ukraine, because of an imprecise gyneacological operation. As comorbidities, she referred to rosacea acne from 2007 with recurring relapses but however she did not take regular medicine. She has been in Italy since 2009 and she is a care worker in a rest home. Baseline exams are reported in (Table 1). Abdomen ultrasound (US) showed light steatosis, Fibro Scan reported LSM equal to 7.4 kPa (IQR 1). Considering the patient's motivation, she started dual therapy as follows: peg-interferon alfa-2a 180 mcg once weekly sc (subcutaneously) plus ribavirin 200 mg 2 cpr+3 cpros (twice daily) (patient's body weight was 65 kg) for 4 weeks (lead-in). At 4th week of dual treatment, HCV RNA was equal to 682 UI/ml and she did not experience adverse skin reaction. Given typical skin side effects with telaprevir and her personal history with acne, we added boceprevir 200 mg 4 cptid every 8 hours with a snack. After 4 weeks of triple therapy, HCV RNA was negative with well-established eRVR and she concluded 28 weeks of antiviral therapy obtaining SVR12 and SVR24. Concerning the side effects, we mentioned asthenia, aneamia, dysgeusia and bronchitis with fever with neutropenia and at the 10th week of triple therapy an extended erythema on the back and on the trunk (Figure 1,2) resolved with steroidal topical cream. At the conclusion of therapy, she had a relapse of rosacea acne needing prolonged antibiotic therapy with tetracycline (Figure 3).

Table 1: Baseline exams of the first patient.

	Baseline value
WBC (10^3/mmc)	5.75
Hb (g/dl)	13.0
MCV (fL)	92
PLT (10^3/mmc)	269
AST (U/L)	30
ALT (U/L)	56
GGT (U/L)	20
ALP (U/L)	51
TOTAL BILIRUBIN (mg/dl)	0.8
DIRECT BILIRUBIN (mg/dl)	0.2
TOTAL PROTEIN (ALB, GAMMA) (g/dl)	8.0 (60%, 16%)
INR	0.6
GLYCEMIA (mg/dl)	83
TOTAL CHOLESTEROL (mg/dl)	175
TRIGLYCERIDE (mg/dl)	53
IL28Brs12979860 genotype	CT
CRYOGLOBULINE/CRYOCRIT	absent
αFP (ng/ml)	12.5
HCV RNA (UI/ml)	448200
CREATININ (mg/dl)	0.6
TSH (mU/L)	0.90
AMA	negative
ASMA	negative
aLKM	negative
ANA	negative
ENA	negative
SIDEREMIA (mcg/dl)	120
TRANSFERRIN (mg/dl)	300
FERRITIN (ng/ml)	80
% TRANSFERRIN SATURATION	30
HIVAb	negative
HBsAg	negative
HBcAb	negative
HBsAb	negative

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

CASE PRESENTATION 2

A 63-years old Italian woman was sent to our department for HCV-related chronic liver disease (genotype 1b) with signs of portal hypertension (oesophageal varices F1). She reported dental care in the 1990s with incidental discovery of hypertransaminasemia in 1997 and on that occasion, she underwent liver biopsy reporting chronic hepatitis (HAI 8) with moderate grade of fibrosis (score 1-2 sec Knodell). In 2006, she

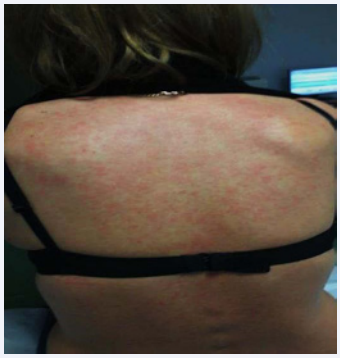

Figure 1 Extended erythema on the back (first patient).

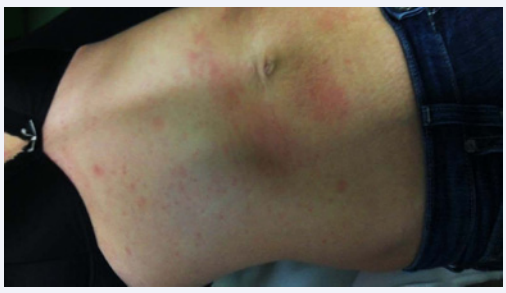

Figure 2 Extended erythema on the trunk (first patient).

underwent a second liver biopsy, which was worse, comparing grading and staging (HAI 11-12, score 4-5 sec Knodell), to that performed in 1997. Concerning previous antiviral treatment, in 1997 she experienced monotherapy with interferon three times subcutaneously weekly for 48 weeks without virological response. Then, in 2004 she started dual therapy (pegylated interferon plus ribavirin at adequate dosage for the patient's body weight), which was stopped after 24 weeks of therapy because of no response. Finally in 2008, she experienced dual therapy again, adding amantadin but the result was the same as in 2004. The former antiviral treatments were generally well tolerated, excepting for aneamia and itching in absence of skin adverse reactions. At our Hepatology Department on November 2013 we performed FibroScan with LSM equal to 37.4 kPa (IQR 2.7) and abdomen ultrasound showing hypertrophy left lobe without focal lesions or splenomegalia. EGD (esophago- gastroduodenoscopy) confirmed single oesophageal varices F1. For the history of high blood hypertension from 2004, she had been taking nebivololo 5 mg 1 c die. We repeated an echocardiogram, which was normal. Baseline exams are reported in (Table 2). Considering the previous null response and staging equal to F4, we started lead-in changing from nebivololo to propanolol because of drug interactions with boceprevir. We planned antiviral treatment as follows: peg-interferon alfa-2b 100 mcg once weekly sc (subcutaneously) plus ribavirin 200 mg 2 CPR+3 cpros (twice daily) (patient's body weight was 70 kg) for 4 weeks. After lead-in, we reported a decrease of 2 log vs. baseline and we added boceprevir 200 mg 4 c tid every 8 hours with a snack. At the 4th week of triple therapy, HCV RNA was equal to <15 UI/ml and there were no adverse skin reactions. At the 10th week, a macular-papular erythema on the arms, legs and trunk (Figures 4-8) appeared. Going on with triple therapy, we started steroidal systemic therapy obtaining resolution of the lesions. However at the 12th week, the patient experienced dyspnea with palpitation of the heart and declivous edema. We performed ECG, which showed atrial fibrillation at high ventricular rate and in the exams we registered values of haemoglobin equal to 8 g/dl, in spite of decreased dosage in ribavirin and supplementation of epoietinaal fasc weekly. The second echocardiogram appeared deteriorated and the patient was suffering greatly, so we stopped triple therapy without virological response. However, afterwards, the cardiologist optimized the therapy and the patient is currently well.

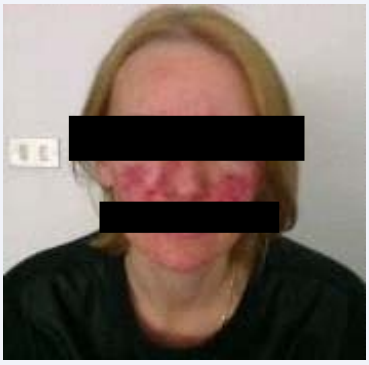

Figure 3 Rosacea acne (first patient).

Table 2: Baseline exams of the second patient.

	Baseline value
WBC (10^3/mmc)	4.53
Hb (g/dl)	14.4
MCV (fL)	100
PLT (10^3/mmc)	164
AST (U/L)	118
ALT (U/L)	129
GGT (U/L)	121
ALP (U/L)	80
TOTAL BILIRUBIN (mg/dl)	1.3
DIRECT BILIRUBIN (mg/dl)	0.4
TOTAL PROTEIN (ALB, GAMMA) (g/dl)	8.4 (49%, 27%)
INR	1.14
GLYCEMIA (mg/dl)	98
TOTAL CHOLESTEROL (mg/dl)	165
TRIGLYCERIDE (mg/dl)	108
IL28Brs12979860 genotype	CT
CRYOGLOBULIN/CRYOCRIT	present/2%
αFP (ng/ml)	32.4
HCV RNA (UI/ml)	175200
CREATININ (mg/dl)	0.64
TSH (mU/L)	0.99
AMA	negative
ASMA	160
aLKM	negative
ANA	negative
ENA	negative
SIDEREMIA (mcg/dl)	250
TRANSFERRIN (mg/dl)	233
FERRITIN (ng/ml)	357
% TRANSFERRIN SATURATION	75
TEST HFE	negative
HIVAb	negative
HBsAg	negative
HBcAb	negative
HBsAb	>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

DISCUSSION

These two case reports underline the complexity of triple therapy with boceprevir concerning skin adverse reactions and other side effects such as anaemia, dyspnea, dysgeusia and leucopenia with high risk of infection. Unfortunately, only the first patient reaches virological response. In our opinion,

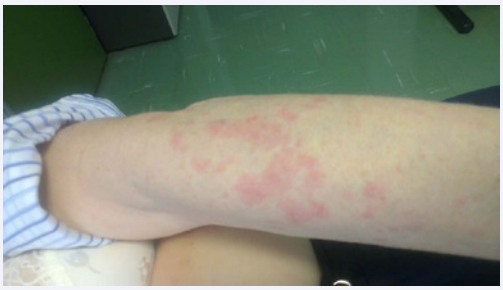

Figure 4 Macular-papular erythema on the arms (second patient).

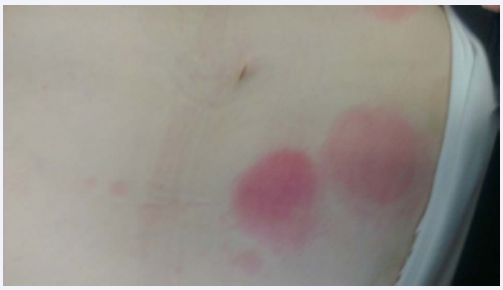

Figure 5 Macular-papular erythema on the trunk and on the back (second patient).

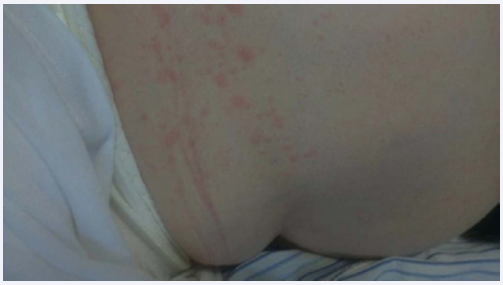

Figure 6 Macular-papular erythema on the trunk and on the back (second patient).

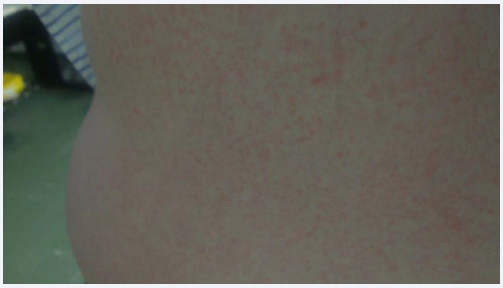

Figure 7 Macular-papular erythema on the trunk and on the back (second patient).

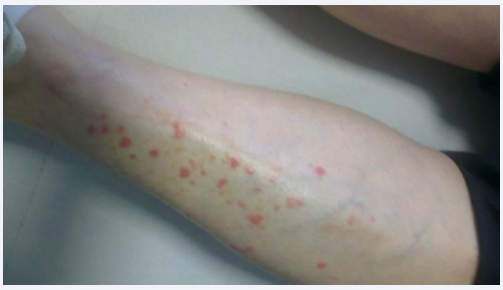

Figure 8 Macular-papular erythema on the legs (second patient).

the other one is considered "difficult to treat" because of null responder in a case of cirrhosis. Both in the first and in the second case the adverse skin reaction appeared later, generally after 8-10 weeks therapy with boceprevir. In the second case we did not stop antiviral treatment because of dermatitis but because of heart condition, probably deteriorated by interferon. The problem of the skin toxicity can be different (from light to severe) but steroidal therapy (systemic or/and topical) often ameliorates. The role of the lead-in phase is important for the detection of early dermatological lesions and thereafter, if the patient has already experienced dual therapy, it is necessary to research previous skin side effects in his/her personal history.

CONCLUSIONS

The hepatologist has to pay attention and has to do frequent monitoring in patients receiving boceprevir. Furthermore, the previous experiences with triple therapy help the clinician to manage following cases more effectively, but, currently, with the arrival of new second generation DAAs, the situation will surely become easier.

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