Therapeutics, Pharmacology and Clinical Toxicology
Vol XVII, Number 4, December 2013
Pages: 207 - 210

TRIPLE THERAPY IN HCV CHRONIC HEPATITIS

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Abstract. Background. As chronic HVC infection is one of the most common infections worldwide, with significant impact on morbidity and mortality, it is important to study the possible curative treatments and their prognostic factors. Triple therapy with interferon, ribavirin and a protease inhibitor (boceprevir) is an important step in the management of HVC positive patients who do not respond to double therapy. We present response rates and predictive factors of the triple therapy with Peginterferon + Ribavirin + Boceprevir. **Methods.** We included 27 patients with treatment failure to the initial therapy. We initially determined their IL28B genotype, viremia, degree of fibrosis and the response type to the initial therapy. On follow-up we tested their viremia at 4, 8, 12, 24, 48 and 72 weeks after the start of triple therapy. **Results.** Sustained Virologic Response (SVR) was achieved in four patients from the seven patients who have reached the 6 month period from the end of the treatment. The remainder of three patients had relapse after receiving the triple therapy. Seventeen patients (77.27%) had undetectable plasma levels of HCV RNA at week 48. An undetectable HCV RNA level was not achieved by treatment week 24 in three patients (13,63%) and all their therapy was discontinued. Also, all treatment was discontinued in two patients before week 24 due to severe adverse events. **Conclusion.** IL28B genotype, degree of fibrosis and type of response to previous therapy can be associated in order to predict the virologic response to triple therapy in HCV infection.
Keywords: HCV chronic infection, triple therapy, IL28B

Background

It is estimated by the World Health Organization that approximately 170 million individuals, are infected with HCV [1]. With the current standard of care, only 40% to 50% of genotype 1–infected patients achieve a sustained virologic response (SVR) [2-4], which leads to a steadily increasing pool of patients termed "nonresponders" who have limited retreatment options and low SVR rates to current standard-of-care treatment options. These patients will contribute to the increase in mortality and morbidity associated with chronic HCV infection. Although we currently rely on interferon and ribavirin therapy [5], there are many new antiviral agents that are under investigation. The highest interest has been around those impacting the replication assembly, and much talk has been about the polymerase inhibitors, the protease inhibitors, and the NS5A and NS4 inhibitors. Romanian Association for the Study of the Liver performed a cross sectional study of B, C, D and E hepatitis viral infection in the south-eastern part of Romania **:** in our country we found a prevalence of *4.56% of HCV chronic infection [6].* Boceprevir is a hepatitis C virus nonstructural protein NS3/4A protease inhibitors (PIs) [7]. It is indicated for the treatment of patients with genotype 1 HCV who have either not previously received treatment or who have failed to attain SVR with previous therapy.

Methods

The objectives of this study were to analyse the efficacy and the safety of the therapy with boceprevir in combination with peginterferon and ribavirin. We also aimed to evaluate the factors which may influence the virologic response rates. Eligibility criteria were: age over 18 years, F3-F4 degree of liver fibrosis, and a previous antiviral treatment. We defined patients as relapsers (patients with undetectable HCV RNA at end of previous treatment with subsequent detectable HCV RNA 6 months posttreatment), partial responders

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(patients with > 2 log decline in HCV RNA by Week 12 of previous therapy but never achieved undetectable HCV RNA), and null responders (< 2 log decline in HCV RNA by Week 12 of previous therapy). Exclusion criteria included: F1-F2 degree of fibrosis, platelet count under 100000/mm^3, Hemoglobin levels under 10mg/dl or chronic HVB infection. Twenty-seven patients were enrolled in this prospective study between September 2011 and September 2012 and began treatment with a 4-week lead-in regimen of peginterferon alpha2b 1,5 μg per kilogram of body weight once weekly and ribavirin at a divided daily dose of 600 to 1400mg per day depending on body weight. After four weeks Boceprevir 800 mg every eight hours with food was added for the next forty-four weeks. For all patients treated with boceprevir, the following futility rules were employed:

1. If HCV RNA is ≥ 100 IU/mL at Week 12, all 3 medications should be discontinued. 2. If the patient has confirmed, detectable HCV RNA at Week 24, all 3 medications should be discontinued. All patients signed an informed consent before starting the treatment. We determined the initial viral load, as well as IL28B genotype, degree of fibrosis, and we determined the type of response of the initial double therapy (null responders or relapsers). Plasma HCV RNA levels were measured at four, eight, twelve, twenty four, forty eight and seventy two weeks. Adverse events were monitored by periodical medical examinations and blood tests. Statistical analysis was performed using SPSS, Cox univariate and multivariate regression.

Results

Baseline characteristics

A total of 27 patients were enrolled, with a mean age of 53.88 years +/- 9.63years. Male to female ratio was 13/14. Regarding the type of response to the previous therapy, there were 14 relapsers and 13 null responders. The ratio between patients with F3 fibrosis and patients with F4 fibrosis was also balanced- 13 patients with F3 degree of fibrosis, 14 patients with F4 degree of fibrosis. After determining the IL28B genotype we concluded that there were 6 patients with TT genotype and 21 patients with CT genotype. No patient had CC genotype. At the moment, out of the twenty seven patients enrolled, five are still in treatment, 7 have completed the treatment and were evaluated at week 72 and fourteen are in the follow up period (from week 48 to week 72).

Efficacy:

Sustained Virologic Response (SVR) was achieved in four patients from the seven patients who have reached the 6 month period from the end of the treatment. The remainder of three patients had relapse after receiving the triple therapy. The baseline characteristics of these patients were: one patient with F4 degree of fibrosis, CT IL 28B genotype and no response to the previous therapy; the second one had F3 degree of fibrosis, CT IL28B genotype and relapsed after the previous therapy; the third patient had F3 degree of fibrosis, TT IL28B genotype and relapsed after the previous therapy. An evaluation of treatment effect was performed at week 48 for twenty two patients. Seventeen patients (77.27%) had undetectable plasma levels of HCV RNA. An undetectable HCV RNA level was not achieved by treatment week 24 in three patients (13,63%) and all their therapy was discontinued. Also, all treatment was discontinued in two patients before week 24 due to severe adverse events. Figure 1 presents the viral kinetics for the enrolled patients, who have reached different sages in the study (figure 1). To identify the baseline characteristics (degree of fibrosis, IL28B genotype and type of response to the previous type) that were significantly associated with the achievement of virologic response at week 4, 8 and 12, we used both univariate and

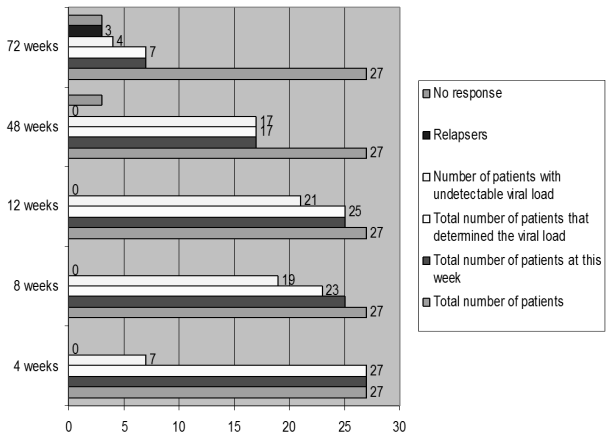

Figure 1. Viral Kinetics

multivariate analysis. In predicting an undetectable viremia at week 4 neither the degree of fibrosis (p = 0.10) nor the previous response type (p= 0.60) have statistic significance. We remark that p value for IL28B genotype is 0.05, which may indicate that this characteristic could serve as a predicting factor. In multivariate logistic regression analysis at week 4 we found no statistically significant influence of degree of fibrosis on the undetectability of RNA HCV no matter what the IL28B genotype is (p = 0.41; F-test= 0.68) but is a good predictor of virologic response depending of the type of response to the previous therapy (p= 0.019, F-test= 6.32). Also IL28B genotype does not influence the virologic response indifferent of the degree of fibrosis (p= 0.179; F- test= 1.92) but it significantly influences the virologic response at week 4, depending on the type of previous response (p = 0.0058; F-test= 9.23). The type of response to the previous therapy is also a statistically significant predictor of the virologic response at week 4, depending on the IL28B genotype (p= 0.038; F-test= 4.80) but indifferent of the degree of fibrosis (p= 0.07; F-test= 3.60). Neither univariate nor multivariate analysis could demonstrate the importance of the degree of fibrosis, IL28B genotype and type of previous response in predicting a virologic response at week 8 and at week 12 (table 1).

Safety

Most notable adverse events occurring more frequently with boceprevir- based therapy are: anaemia (all patients), hyperuricemia (five patients), dyslipidemia (eleven patients), dysgeusia (twenty patients), eruptions (two patients), arrhythmia (one patient), portal decompensation (one patient). Consistent with the high incidence of anaemia, the number of patients with haemoglobin level of 10 to 12 gram per decilitre was 11; haemoglobin 8 to 10 gram per decilitre was found in 10 patients; 6 patients had haemoglobin levels of 6 to 8 gram per decilitre. Erythropoietin was administered to three patients, three patients received blood transfusions. The ribavirin dose reduction was sufficient in six patients for the management of anaemia. At week 5 we report one death: a woman of 50 years with sepsis and septic cerebral metastases from pneumonia. We also report a case of necrotising vasculitis at week 28; the patient discontinued all treatment. However, at week 48 the patient had undetectable viremia.

Discussions

Our data show that the addition of boceprevir to standard peginterferon and ribavirin therapy leads to better response among treatment- experienced patients. Regarding the initial factors (degree of fibrosis, IL28B genotype, type of response to previous therapy) that can influence the response to the treatment, uni and multivariante analysis have demonstrated a statistically significant association in the following cases. The degree of fibrosis influences the virologic response in correlation with the response to the previous therapy. IL28B genotype influences the virologic response depending on the type of response to the previous therapy. The type of previous response can predict the virologic response in association with the IL28B genotype. We remark that these correlations are only valid for week 4 evaluation. IL28B has been found to be a reliable predictor alone in other studies [8]. The four-week lead in period allowed us to determine the patients' responsiveness to interferon before the addition of boceprevir. Bacon, Gordon et all [9] report an incidence of anaemia of 43-46% in their boceprevir group. We found that in our group of study the incidence of anaemia was 100%. Despite this high rate, anaemia was not the cause of treatment disruption in any of the patients. Adverse

	Week 8	**Week 12**
Univariate analysis	IL28B genotype (p= 0.26) Previous response (p=0.80) Degree of fibrosis (p= 0.75)	IL28 B genotype (p= 0.33) Previous response (p= 0.50) Degree of fibrosis (p= 0.39)
Multivariate analysis	IL28B genotype+ Previous response (p= 0.237 respectively p= 0.61266)	IL28 B genotype + Previous response (p= 0.489 respectively p= 0.906)
	IL28B genotype + Degree of fibrosis (p= 0.083 respectively p= 0.173)	IL28 B genotype + Degree of fibrosis (p= 0.596 respectively p= 0.755)
	Previous response + Degree of fibrosis (p= 0.154 respectively p= 0.151)	Previous response + Degree of fibrosis (p= 0.740 respectively p= 0.532)

Table I. P values for univariate and multivariate analysis for possible predictors of virologic response.

events imposed discontinuation of the treatment in two cases: a 70 year old patient with severe portal decompensation of cirrhosis and a 49 year old patient with crioglobulinemic vasculitis and sepsis resulting in death. Similar data are reported by Hézode et all in the Cupic study [10]. More work will need to be done to fully characterize predictors of response and indicators of treatment failure. Having reliable predictors of response may help motivate patients to adhere to treatment. Moreover, accurate indicators of null response will help lower the risk of resistance and spare patients from unnecessary treatment and its adverse effects and potentially keep the door open for future treatment options.

Conclusions

- The degree of fibrosis influences the virologic response in correlation with the response to the previous therapy.
- IL28B genotype influences the virologic response depending on the type of response to the previous therapy.
- The type of previous response can predict the virologic response in association with the IL28B genotype.
- We found that in our group of study the incidence of anaemia was 100%.

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