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Personalized cost-effectiveness of boceprevir-based triple therapy for untreated patients with genotype 1 chronic hepatitis C

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ABSTRACT

Background: We assessed the cost-effectiveness of boceprevir-based triple therapy compared to peginterferon alpha and ribavirin dual therapy in untreated patients with genotype 1 chronic hepatitis C; patients were discriminated according to the combination of baseline plus on-treatment predictors of boceprevir-based triple therapy.
Methods: Cost-effectiveness analysis performed according to data from the available published literature. The target population was composed of untreated Caucasian patients, aged 50 years, with genotype 1 chronic hepatitis C, and these were evaluated over a lifetime horizon by Markov model. The study was carried out from the perspective of the Italian National Health Service. Outcomes included discounted costs (in euro, at 2013 value), life-years gained, quality-adjusted life year, and incremental cost-effectiveness ratio. The robustness of the results was evaluated by multivariable probabilistic sensitivity analyses.
Results: According to the baseline predictors of sustained virological response (genotype 1b, low viral load, fibrosis F0-F3, and body mass index) and the 1 Log drop of HCV-RNA after the dual therapy lead-in period, boceprevir was cost-effective in different patient profiles.
Conclusions: In untreated genotype 1b chronic hepatitis C patients, the cost-effectiveness of boceprevir-based triple therapy widely ranges according to different profiles of sustained virological response predictors, allowing optimization and personalization of triple therapy.

1. Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide, and it has reached a pandemic spread, with an estimated prevalence of 2.2% worldwide, and of 0.6–5.6% in Europe [1,2]. This is of increasing interest not only because HCV is one of the main causes of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease in Western countries, but also due to the fact that achievement of a sustained virological response (SVR) prevents not only the development of cirrhosis in patients with chronic hepatitis C (CHC) [3], but also, in subjects with cirrhosis, the occurrence of its complications, such as oesophageal varices [4] and liver-related death [5], also reducing HCC occurrence [6].

In the last few years the standard of care for untreated genotype 1 (G1) CHC patients changed from dual therapy (DT) with peginterferon alpha (PEG-IFN) and weight-based ribavirin (RBV), to triple therapy (TT) with PEG-IFN, RBV, and the first-generation NS3-NS4 HCV protease inhibitors (PI) boceprevir or telaprevir [7]. Registrative randomized controlled trials (RCTs), namely SPRINT2 and ADVANCE [8,9], showed that a course of 12–44 weeks of a first-generation PI combined with 24–48 weeks of PEG-IFN plus RBV, with the duration of therapy guided by the on-treatment response and the presence of cirrhosis, provided a gain in SVR rate of about 25% compared with DT. Accordingly, we demonstrated that TT with first-generation PI is a highly cost-effective treatment

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in untreated G1 CHC patients [10]. However, all the above quoted results arise from aggregate rather than individual patient data, consequently reflecting group averages rather than individual data. In addition, TT therapy is at risk for the development of resistance, has a poor tolerability profile especially in cirrhotic patients [11], and is characterized by the issue of drug interactions and the long-term complicated regimens with high pill burdens.

In untreated G1 CHC patients, boceprevir, but not telaprevir, were used with a lead-in period of 4 weeks of DT before starting TT, to test the sensitivity to IFN, a strong predictor of SVR for both DT and TT. Accordingly, a recent post hoc analysis of the SPRINT-2 RCT [12] identified the following parameters as independent predictors of SVR: F0-F3 fibrosis, LVL, G1b, absence of obesity, and >1 Log drop in HCV-RNA after the lead-in period. These variables, available for boceprevir, but not for telaprevir, could be used to identify different profiles of patients with different likelihood of SVR to boceprevir-based TT, allowing personalization and optimization of boceprevir-based antiviral therapy.

With this in mind the aim of this analysis was to determine the cost-effectiveness of boceprevir-based TT compared to DT in untreated patients with G1 CHC, discriminated according to the combination of baseline plus on-treatment predictors of boceprevir-based TT.

2. Methods

2.1. Study population

We performed a cost-effectiveness analysis according to data from the available published literature (SPRINT 2 [8] and IDEAL [13] RCTs). Our base-case was a hypothetical cohort of Caucasian male patients, 50 years old, discriminated according to baseline predictors of SVR to boceprevir-based TT combined with week-4 IFN sensitivity. The base-case represents the prototype of patients enrolled in SPRINT 2 [8] and IDEAL [13] RCTs, in which data for cost-effectiveness analyses were recorded.

2.2. Structure of the model

We assumed that SVR eliminates the risk of developing progressive liver disease [4,14,5,6] in CHC patients. Instead, in patients with cirrhosis, we considered a residual risk for HCC [15]. We used a semi-Markov model to simulate the natural history of CHC in the non-treated patients and in the non-responder group of each treatment strategy over a lifetime horizon. Annual cycles were considered with a half-cycle correction [16]. Independently of the treatment option chosen, patients could follow one of three different paths in each 1-year cycle, based on their transition probabilities: (a) continue in the same health state without suffering from any event; (b) have a liver-related event (i.e., variceal bleeding, HCC, ascites, encephalopathy, jaundice); or (c) die of a liver-related cause.

Since the study is conducted over a lifetime horizon, deaths from other causes are implicitly taken into account by using age-related mortality rates from the National Institute of Statistics (ISTAT) [17] in CHC and cirrhotic patients only. All patients suffering from an acute event could die during that year (liver-related death) or survive (at least for that year). The health states were mutually exclusive, i.e., a patient could only experience one health state at any given time. Transition probabilities were taken from previously published studies [18–22] that used survival curves, cumulative risk functions, or aggregate data published in the literature (the average annual probability of transition is given in Table 1). These survival curves were reproduced using a Weibull distribution for each transition. The transition probability from CHC to compensated cirrhosis was assumed to depend linearly on time [23], i.e. each patient experiences a constant annual progression rate of fibrosis, without any difference in the annual fibrosis progression rate. Cross-model validation was performed by comparing differences in the outcomes generated by our model with those of other models. The 30-year cumulative probability of developing compensated cirrhosis for the base-case patients of our model (male, 50 years old, fibrosis F2) was 42%. This number is consistent with the results from other studies [24–26] reporting mean rates from 25% to 32% in 40-year old men with F0 fibrosis. In addition, our model produced a rate of death for compensated cirrhosis of 7.5%, and for decompensated cirrhosis and HCC of 34.7% (30.2% for decompensated cirrhosis and 4.5% for HCC), being this last figure similar to the 32.5% determined with the model used by Rein et al. [27].

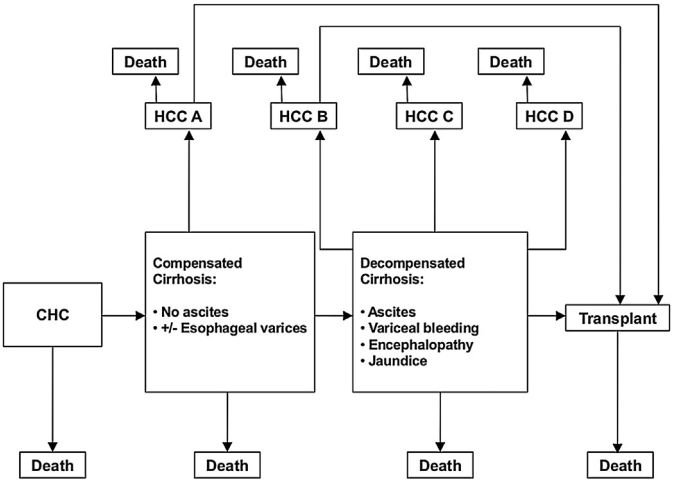

Fig. 1. Schematic of the Markov Model. Every year, patients can move between heath states in the model according to a defined transition rate. Patients in both chronic hepatitis and cirrhosis states can move to death due to both liver and not liver-related causes, while the other states due to liver-related causes only. CHC, chronic hepatitis C; HCC, hepatocellular carcinoma.

Model creation and analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) [28] and Microsoft Excel 2007 software (Microsoft, Redmond, WA, USA). Fig. 1 shows the basic format of the model.

2.3. Treatment strategies, effectiveness and Quality of Life data

By considering baseline predictors of SVR to boceprevir-based TT [12] (F0-F3 fibrosis, LVL, G1b, and absence of obesity) and the 1LOG HCV-RNA drop after the lead-in period, we obtained 32 different clinical profiles.

In each group, patients in arm 1 of the model received boceprevir-based TT, while patients in arm 2 received DT. Effectiveness data arising from the SPRINT-2 RCT [8] for boceprevir and from the IDEAL RCT [13] for the DT are summarized in Supplementary Table S1. The likelihood of SVR in each group was estimated by multivariate logistic models. To estimate the expected probability of SVR for a hypothetical patient with a combination of predictors of response the logit function was computed. Significant variables in the multivariate models of SVR rate after DT and TT were used to generate a prediction rule. For each case, a probability of SVR was calculated giving a set of values for all the significant predictors of response in the multivariate models. The main statistical methods for the logit function and logistic regression have been described elsewhere [29].

In all the evaluated profiles, DT includes PEG-IFN alpha-2b at a dose of 1.5 μg/kg weekly, or PEG-IFN alpha-2a at a dose of 180 μg