
Original article

Individualized treatment of HBeAg-negative chronic hepatitis B using pegylated interferon-α2a as first-line and week-12 HBV DNA/HBsAg stopping rule: a cost-effectiveness analysis

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Background: Hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) is the most frequent and difficult-to-treat viral hepatitis worldwide. HBV DNA and hepatitis B surface antigen (HBsAg) serum levels, which help the early identification of non-responders to pegylated interferon (PEG-IFN), prompt more flexible individualized therapeutic strategies exploiting the benefits of both PEG-IFN and nucleoside/nucleotide analogues (NAs). We assessed the cost-effectiveness of week-12 HBV DNA/HBsAg stopping rule for early interruption and switch to currently most effective NA treatments (entecavir [ETV] or tenofovir disoproxil fumarate [TDF]).

Methods: A decision-analytic Markov model was developed in the following health-related states: CHB, compensated cirrhosis (CC) and decompensated cirrhosis, hepatocellular carcinoma, liver transplant, post-liver transplant, death, virological response, relapse and HBsAg clearance. Simulated strategies included: ETV/TDF in CHB; ETV/TDF delayed until CC; first-line PEG-IFN followed by switch to ETV/TDF for either patients meeting the week-12 stopping rule or week-48 null-responders/relapsers; and first-line PEG-IFN followed by switch to ETV/TDF delayed until CC. ETV and TDF were considered alternatively for a total of eight strategies. A lifetime simulation horizon was applied.

Results: Early treatment strategies using NAs with or without first-line PEG-IFN provided the highest results (approximately 22 life-years and 15 quality-adjusted life years [QALYs]). Delayed treatments until cirrhosis development resulted in poorer outcomes. The average per-patient lifetime costs ranged from €33,500 (TDF in CC) to €68,900 (TDF in CHB). Costs using ETV were 20–50% higher. First-line PEG-IFN strategies ranged from dominant (that is, more effective and less costly) to highly cost-effective, although differences in QALYs were always very narrow.

Conclusions: The cost-effectiveness of antiviral therapy of HBeAg-negative CHB could be improved significantly using first-line PEG-IFN followed by a switch to NAs in either patients meeting the week-12 HBV DNA/HBsAg stopping rule or week-48 non-responders/relapsers.

Introduction

Although a safe and effective vaccine has been available for >2 decades, HBV infection remains a serious global health concern, with 2 billion individuals infected and >350 million chronic hepatitis B (CHB) surface antigen (HBsAg) carriers [1–3]. There are two forms of CHB, namely hepatitis B e antigen (HBeAg)-positive and HBeAg-negative. The latter is caused by HBeAg-defective HBV mutants and has been more frequently reported in Mediterranean areas, where it appears to prevail among genotype-D-infected patients [3,4]. Currently, HBeAg-negative CHB is considered a major burden globally because of its strong correlation with the risk of cirrhosis and hepatocellular carcinoma [5].
The goal of hepatitis B therapy is the remission of liver disease and, ultimately, prevention of cirrhosis, liver failure, hepatocellular carcinoma (HCC) and death. As clinical outcomes can take decades to develop, assessment of treatment response relies on intermediate outcomes, including the decrease of HBV DNA serum levels, drop and clearance of circulating HBsAg, normalization of serum alanine aminotransferase (ALT) levels, and a decrease in hepatic inflammation [1–3,6,7]. Currently, seven treatments have been approved for hepatitis B, including two formulations of interferon (standard interferon and pegylated interferon [PEG-IFN]-α2a) and five nucleoside analogues (lamivudine, adefovir dipivoxil, telbivudine, tenofovir disoproxil fumarate [TDF] and entecavir [ETV]). Nucleoside analogues (NAs) are, in general, well tolerated and the newest, ETV and TDF, are associated with a very low incidence of antiviral resistance [3]. However, in HBeAg-negative CHB, as with lamivudine, they have to be administered indefinitely or on a lifetime basis since they are unable to induce a sustained immune control of HBV infection after withdrawal, even after years of continuous administration. The alternative therapeutic option is a finite (48 weeks) course of treatment with PEG-IFN-α2a, which can induce the sustained immune control of HBV infection after the end of treatment with clearance of HBsAg after years of treatment, but has the disadvantages of a limited response rate (20–30%) in HBeAg-negative CHB and of subcutaneous weekly injections [6,7]. Recent studies showed that a lack of reduction of serum levels of HBsAg in addition to those of HBV DNA at week 12 of PEG-IFN treatment is associated with failure to respond at the end of the treatment [8–11]. Such findings lead the way to the early identification of non-responders (stopping rule) for a more flexible and individualized therapeutic approach, which exploits the benefits of using both PEG-IFN and NAs.

Methods

A decision-analytic Markov model was used to simulate outcomes and associated costs in both natural and therapy-associated history of HBeAg-negative CHB and its progression to end-stage liver disease complications.

Natural history model: simulation flow

The model simulated a population of HBeAg-negative CHB patients. Figure 1 depicts a simplified representation of the model: all patients started in the active phase of chronic HBeAg-negative HBV infection.

As we know from studies on the natural history of the disease, spontaneous (that is, without pharmaceutical treatment) recovery of HBeAg-negative CHB and serum HBsAg clearance are unlikely [1,2]; thus, it was assumed that the spontaneous switch of CHB to the inactive carrier phase or HBsAg clearance could not occur. Virological response was defined according to the European Association for the Study of the Liver (EASL) clinical guidelines [1]: when treating with an NA, as undetectable HBV DNA by a sensitive PCR assay and when treating with PEG-IFN, as HBV DNA serum levels of <2,000 IU/ml (approximately corresponding to 10,000 copies/ml).

The disease progressed through different stages of clinical severity, including compensated and decompensated cirrhosis, hepatocellular carcinoma and liver transplant; it was assumed that hepatocellular
Carcinoma could only develop from a cirrhotic state. Disease-specific death could occur from each health state starting from cirrhosis; these stages were associated with a different probability of death depending on the severity of the underlying liver disease. All-cause mortality was also taken into consideration in every disease state, defined as death from any cause not directly attributable to CHB.

Treatment model
The treatment goal is to turn the HBeAg-negative CHB patient into an inactive HBsAg carrier and eventually develop HBsAg seroclearance. Eight different strategies that included first-line treatment with PEG-IFN with the option of early interruption at week 12 and switch to TDF or ETV for patients who meet the stopping rule criteria, and late switch for 48-week null-responders/relapsers and NA monotherapies were considered (Table 1). Treatment with ETV or TDF was assumed to stop only after HBsAg clearance or death. The rationale for not considering the whole range of analogue products was that ETV and TDF demonstrated to be the most effective and widely used in clinical practice [12,13].

Stopping rule
The stopping rule during treatment with PEG-IFN was based on the results of the study by Rijckborst et al. [10], which were recently validated in an external data set [14]. The evidence was based on a total of 102 HBeAg-negative patients enrolled in the PARC trial [15] who were treated with PEG-IFN (with or without ribavirin) for 48 weeks, and who completed the post-treatment follow-up phase of 24 weeks and had serum HBsAg and HBV DNA levels available at baseline and at week 12. The study reported that none of the 20 (out of 102) patients who, from baseline to week 12, did not show any detectable decrease in serum HBsAg and an HBV DNA decrease <2 log, achieved sustained virological response. Sustained virological response was defined as HBV DNA <2,000 IU/ml (approximately 10,000 copies/ml) and normal ALT after 24 weeks of post-treatment follow-up. External validation of this rule was performed on 85 patients treated with PEG-IFN monotherapy for 48 weeks in a Phase III registration trial [7], and 75 patients treated with PEG-IFN monotherapy for 48 or 96 weeks in the PegBeLiver study [16]. In this confirmation study [14] only one patient of the 22 who did not demonstrate a detectable decrease in serum HBsAg and an HBV DNA decrease <2 log at week 12, achieved sustained response. By pooling the two studies, an overall 16.0% of the tested patients met the early responder conditions. The application of the stopping rule in the model was defined as follows: all simulated patients on treatment with PEG-IFN were tested at week 12; 16% of them met the stopping-rule conditions (no decrease in serum HBsAg and an HBV DNA decrease <2 log) and discontinued PEG-IFN treatment.

Adverse events
Adverse events were not included in this analysis. General safety data collected in real-life studies confirmed in the long run the safety outcomes observed

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
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<tbody>
<tr>
<td>TDF in CHB</td>
<td>Patients were immediately treated with TDF. No second-line treatment was foreseen due to high response rates to this analogue.</td>
</tr>
<tr>
<td>TDF in CC</td>
<td>Patients did not receive any antiviral therapy until their CHB progressed to compensated cirrhosis, when they started treatment with TDF. As for the TDF in CHB strategy, no second line was foreseen.</td>
</tr>
<tr>
<td>PEG-IFN plus TDF in CHB</td>
<td>Patients received PEG-IFN as first-line treatment. The stopping rule was applied so that all patients were tested at week 12 for early identification of non-responders based on quantitative HBV DNA and HBsAg assays: patients meeting the stopping criteria discontinued PEG-IFN and started a second-line treatment with TDF, whereas the remaining completed the 48-week treatment with PEG-IFN.</td>
</tr>
<tr>
<td>PEG-IFN plus TDF in CC</td>
<td>Patients not achieving an end-of-treatment response or relapsing thereafter switched to TDF in second-line treatment.</td>
</tr>
<tr>
<td>ETV in CHB</td>
<td>This strategy was similar to PEG-IFN plus TDF in CHB with the difference that patients interrupting PEG-IFN at week 12 or not showing end-of-treatment response did not start a second-line treatment with TDF until cirrhosis developed.</td>
</tr>
<tr>
<td>ETV in CC</td>
<td>This strategy was similar to TDF in CHB, with ETV instead of TDF.</td>
</tr>
<tr>
<td>PEG-IFN plus ETV in CHB</td>
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<td>PEG-IFN plus ETV in CC</td>
<td>This strategy was similar to PEG-IFN plus TDF in CC, with ETV instead of TDF.</td>
</tr>
</tbody>
</table>

CC, compensated cirrhosis; CHB, chronic hepatitis B; ETV, entecavir; HBsAg, hepatitis B surface antigen; PEG-IFN, pegylated interferon; TDF, tenofovir disoproxil fumarate.
in clinical trials, with <6% of patients stopping treatment due to adverse events [17–19].

Data and sources
A systematic review of the literature was performed to populate the model with data inputs. The databases searched were Medline, EMB reviews (including the Cochrane database) and the EMBASE database via the OVID SP platform. Only articles written in English and published between January 2004 and June 2012 were considered. A further manual search was conducted among abstracts and proceedings of recent clinical congresses of the EASL, Asian Pacific Association for the Study of the Liver (APASL) and American Association for the Study of Liver Diseases (AASLD).

Health outcomes
The probability of achieving virological response and HBsAg clearance after the end of the 48-week PEG-IFN course was derived from the interim report of the S-Collate study, a multicentre, prospective, non-interventional ‘real-life’ cohort study on 683 HBeAg-negative patients [17]. The probabilities of achieving virological response and HBsAg clearance in the long term (from the second year onwards) were derived from the 5-year extension observational study of the Phase III randomized controlled trial of PEG-IFN [7], which enrolled 230 patients previously treated with PEG-IFN, with or without the addition of lamivudine, in a 48-week course [20]. Observed rates were adapted to account for the simulated adoption of the stopping rule. It was assumed that no patient with a negative test at week 12 (16% of the cases) would achieve a virological response from the second year onwards and eventually clearance of HBsAg. Thus rates for year 2 onwards were recalculated excluding patients with a negative test. Response rates are reported in Table 2.

Virological response rates were 90.2% with ETV [12] and 93.2% with TDF [13] after 1 year of treatment. Data beyond 1 year could be obtained from two observational studies on NA-naive Italian patients treated with ETV (n=418) and TDF (n=302), followed-up for a total of 54 [18] and 36 [19] months, respectively. The observed response rates reached 100% after 4 years with ETV and 98% after 3 years with TDF. Long-term data were not available to suitably simulate the probability of HBsAg clearance from the virological response to antiviral agents. In the TDF observational study [19], two patients in the HBeAg-negative subgroup reached HBsAg clearance at year 3. Based on this finding, we assumed a 0.4% annual probability of HBsAg clearance when in the virological response state. We assumed the same probability for ETV. This figure is close to what was previously used (1%) in other published models for all NAs [21,22].

Health state transition probabilities (Table 2) from compensated cirrhosis health state onwards were derived from published literature [21–26] and were not assumed to be dependent on pharmacological efficacy; therefore, when a patient reached the compensated cirrhosis health state, they were simulated to follow the natural disease progression of CHB.

Costs
Direct medical costs were included in the analysis (Table 2), from the Italian National Health Service perspective. Drug costs were estimated using the price of supplying to public hospitals, including all mandatory discounts [27–29].

The costs associated with the progression of CHB were based on a set of annual costs related to the different severity stages of chronic hepatitis B and C, as recently reported in a publication from the Associazione Italiana per lo Studio del Fegato (AISF) [30]. The AISF study used data from a previous Italian cost study [31] in which diagnosis-related group rates and national tariffs were used to assess the cost of health care resources (for example, hospitalizations, specialized activities and diagnostic activities) associated with each health state and liver disease progression, and inflated them to 2011 levels.

Monitoring costs were estimated on the basis of testing recommendations in the EASL Clinical Practice Guidelines [1] and costed according to current tariffs [32]. The cost related to the performance of the tests (HBV DNA and HBsAg detection) used in the application of the stopping rule, when treating patients with PEG-IFN, was also considered [32].

Quality of life
No data was found regarding quality of life specific to Italian CHB patients. Consequently, health state utility estimates were derived from an international study by Levy et al. [33], which used the standard gamble technique [34] to estimate utilities in a group of 534 hepatitis patients and 600 uninfected respondents, using an interviewer-administered survey in the US, Canada, UK, Spain, Hong Kong and mainland China. For the purpose of this analysis, utilities derived from the Spanish CHB-infected population only were considered (Table 2). Utility associated with the HBsAg clearance state was assumed to be equal to the value of ‘current health’ reported by the uninfected cohort (0.87), as a reference for a ‘normal’ condition.

Analyses
Outcomes considered in the analyses were lifetime discounted costs, discounted life-years, discounted
Table 2. Model inputs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case</th>
<th>OWSA range</th>
<th>PSA distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discount rate costs (annual), %</td>
<td>3.5</td>
<td>0–7</td>
<td>Beta</td>
<td>–</td>
</tr>
<tr>
<td>Discount rate outcomes (annual), %</td>
<td>3.5</td>
<td>0–7</td>
<td>Beta</td>
<td>–</td>
</tr>
</tbody>
</table>

Baseline cohort characteristics

Mean age, years 37.3
Males, % 74.2

Annual transition probabilities

With PEG-IFN

CHB-A to CHB-R in year 1 0.850
CHB-R to CHB-A in year 2 0.636
CHB-R to CHB-A in year 3 onward 0.124
CHB-A to sCL in year 1 0.053
CHB-R to sCL in year 2 0.005
CHB-R to sCL in year 3 onward 0.106

With ETV

CHB-A to CHB-R in year 1 0.902
CHB-R to CHB-A in year 2 0.814
CHB-R to sCL 0.004

With TDF

CHB-A to CHB-R in year 1 0.932
CHB-A to CHB-R in year 2 onward 0.733
CHB-R to sCL 0.004
CHB-A to CC (with no treatment) 0.097
CHB-A to CC (with treatment) 0.048
CHB-R to CC 0.001
CC to DCC 0.035
CC-A to HCC (with no treatment) 0.022
CC-A to HCC (with treatment) 0.014
CC-R to HCC 0.005
CC to death 0.034
DCC to HCC 0.059
DCC to LT 0.026
DCC to death 0.249
HCC to LT 0.250
HCC to death 0.265
LT to post LT 0.85
LT to death 0.139
Post LT to death 0.025

Costs

ETV (Baraclude) 377.7
TDF (Viread) 239.21
PEG-IFN (Pegasys) 167.88
Annual cost of CHB 246.03
Annual cost of CC 347.19
Annual cost of DCC 5,465.88
Annual cost of HCC 6,075.46
Annual cost of LT 150,000
Annual cost of post LT 4,729.29
Cost of monitoring TDF/ETV in year 1 164.02
Cost of monitoring TDF/ETV in year 2 onward 93.68
Cost of PEG-IFN stopping test 28.87
Cost of monitoring PEG-IFN in year 1 208.77
Cost of monitoring PEG-IFN in year 2 102.52
Cost of monitoring PEG-IFN in year 3 onward 58.52

Notes:

a) Also based on assumption. 

All costs are Euros (€). CHB, compensated cirrhosis; CHB-A, compensated cirrhosis with active chronic hepatitis B; CHB-R, compensated cirrhosis with virological response; CHB-A, active chronic hepatitis B; CHB-R, chronic hepatitis B with virological response; DCC, decompensated cirrhosis; ETV, entecavir; HCC, hepatocellular carcinoma; LT, liver transplant; OWSA, one-way sensitivity analysis; PEG-IFN, pegylated interferon-α2a; PSA, probabilistic sensitivity analysis; sCL, clearance of hepatitis B surface antigen; TDF, tenofovir disoproxil fumarate.

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quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) of all treatment strategies. Analyses were performed on a lifetime horizon. Costs and outcomes were discounted at an annual rate of 3.5% (Table 2).

The uncertainty surrounding the input parameters was tested using two types of sensitivity analyses: one-way sensitivity analysis and probabilistic sensitivity analysis. In one-way sensitivity analysis the effect of varying one parameter at a time was tested on the model. This was systematically done by re-running the model simulation on lower and upper bound values of each parameter. The upper and lower bound values were obtained by decreasing and increasing base case values by 20%. The discount rates were tested at 0% and 7%. Since probabilities of achieving HBsAg clearance were considered as having a potentially crucial role in the outcomes of the simulation and given the paucity of data concerning long-term rates measured in clinical studies with PEG-IFN and viral analogues, a specific sensitivity scenario was investigated.

In the probabilistic sensitivity analysis, uncertainty surrounding inputs was tested simultaneously from all parameters to assess the effect on the results. This was done by initially assigning a distribution to all the modelled input parameters. For each input parameter, a random value was then drawn from the respective distribution to estimate the model-intended outcomes and costs. This process was repeated for each of the 1,000 iterations of Monte Carlo simulation. Distributions were fitted to each parameter assuming a standard deviation equal to 10% of the base value.

**Results**

**Base case results**

Results were reported for all strategies in terms of discounted life-years, QALYs and costs (Table 3).

The strategies of early treatment with NAs, with or without a PEG-IFN first-line, gave the highest results in terms of life-years (TDF and ETV in CHB 21.97 and 21.96, respectively; PEG-IFN plus TDF and ETV in CHB 21.65 and 21.68, respectively). The highest numbers of QALYs were given by PEG-IFN plus TDF and PEG-IFN plus ETV in CHB, with 15.29 and 15.31, respectively. Strategies that delayed the treatment with NA until cirrhosis resulted in poorer outcomes for the patient. Strategies that involved ETV, while being very similar in terms of outcome results to their respective ones with TDF, were consistently more expensive. As expected, strategies that delayed the treatment with NAs until the development of liver cirrhosis resulted in lower average costs.

Two sets of comparisons were evaluated for the cost-effectiveness analysis of the considered alternatives.
(Table 4). First was the effect of first-line PEG-IFN. Each strategy involving first-line PEG-IFN was compared with its respective strategy using the same NA as first-line treatment (for example, PEG-IFN plus TDF in CHB versus TDF in CHB). Second was the effect of early versus delayed treatment with NAs. Each strategy considering an initiation of NA treatment in CHB was compared with its respective strategy, defined by the same drug sequence with the initiation of NA treatment in compensated cirrhosis (CC; for example PEG-IFN plus TDF in CHB versus PEG-IFN plus TDF in CC).

In the first set of comparisons (first-line PEG-IFN), strategies with first-line PEG-IFN were always dominant (that is, more effective and less costly) as compared with their respective NA-only strategy. One exception was found in comparing PEG-IFN plus TDF in CC with TDF in CC, which gave an ICER of €1,152.43/QALY (Table 4). It should be noted that in the two comparisons involving the treatment with antivirals in CHB the difference in QALY was very small (approximately 2.1%) and that the difference in life-years had a reversed sign with the NA-only strategies producing a slightly higher survival (difference of approximately 1.5%). This supposedly contradictory effect can be related to the adjustment of survival by the health-state-related quality of life.

In the second analysis perspective (early versus late NA), early NAs strategies always appeared more effective and more expensive than their respective ones with late NA treatment. The ICER ranged from €11,797/QALY for TDF in CHB versus TDF in CC to €20,778/QALY for PEG-IFN plus ETV in CHB versus PEG-IFN plus ETV in CC (Table 4).

Sensitivity analyses results
The sensitivity analyses were performed to test the stability of the model results against the uncertainty of input parameters. To this extent, sensitivity analyses were performed on the comparison PEG-IFN plus TDF in CC versus TDF in CC under the assumption that the other comparisons would have been affected by parameter uncertainty in a similar way.

One-way sensitivity analysis
The one-way sensitivity analysis tested the effect on the ICER of changing one parameter at a time to its upper and lower bound values. After testing these values a tornado diagram was depicted with those parameters affecting the ICER the most (Figure 2). The diagram shows that the response and relapse rates for PEG-IFN yielded the highest effect on the base case ICER (€1,152.43/QALY). Overall the model showed a good stability around base case results.

To address a potential concern around the impact of the assumptions taken to define the probabilities of achieving HBsAg clearance in the medium term, a specific scenario was calculated in which the transition probability from CHB with virological response to clearance of HBsAg at the third year and following with PEG-IFN was set to 0.004 and at the same time that with TDF to 0.106. The ICER of the comparison of PEG-IFN plus TDF in CC versus TDF in CC resulted in €4,726.07/QALY.

Probabilistic sensitivity analysis
A total of 1,000 iterations were run in the probabilistic sensitivity analysis to assess the stability of the model and the robustness of the base case scenario (Figure 3). This was demonstrated by the compact cloud of dots (each the result of one iteration) around the base case ICER at €1,152.43/QALY, corresponding to 1.30 incremental QALYs and to €1,496 incremental cost.

The cost-effectiveness acceptability curve is a commonly used technique to depict the results of the probabilistic sensitivity [35]. It estimates the probability that the treatment is cost-effective compared to the alternative, given a range of cost-effectiveness thresholds. The cost-effectiveness acceptability curve in Figure 4 shows that, while the base case ICER of PEG-IFN plus TDF in CC versus TDF in CC was €1,152.43/QALY, there was an uncertainty associated with it as estimated by the probabilistic sensitivity. The acceptability of this uncertainty is associated with the maximum cost-effectiveness that the decision maker is willing to accept (the threshold). The acceptability of the assessed strategy, expressed as the probability of the treatment being cost-effective over the comparator, can be read on the cost-effectiveness

<table>
<thead>
<tr>
<th>Table 4. Cost-effectiveness analysis</th>
<th>Cost-effectiveness comparisons</th>
<th>ICER, € per QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN first-line</td>
<td></td>
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<tr>
<td>PEG-IFN plus TDF in CHB versus TDF in CHB</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td>PEG-IFN plus TDF in CC versus TDF in CC</td>
<td>1,152.43</td>
<td></td>
</tr>
<tr>
<td>PEG-IFN plus ETV in CHB versus ETV in CHB</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td>PEG-IFN plus ETV in CC versus ETV in CC</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td>Early versus delayed treatment with NAs</td>
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<tr>
<td>TDF in CHB versus TDF in CC</td>
<td>11,796.75</td>
<td></td>
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<tr>
<td>PEG-IFN plus TDF in CHB versus</td>
<td>12,117.99</td>
<td></td>
</tr>
<tr>
<td>PEG-IFN plus TDF in CC</td>
<td>17.99</td>
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<tr>
<td>ETV in CHB versus ETV in CC</td>
<td>20,222.34</td>
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<tr>
<td>PEG-IFN plus ETV in CHB versus</td>
<td>20,778.43</td>
<td></td>
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<tr>
<td>PEG-IFN plus ETV in CC</td>
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</table>

A cost-effectiveness analysis (cost per quality-adjusted life year [QALY]) is displayed for the strategies that included a pegylated interferon-α2a (PEG-IFN) first-line as compared to those based only on nucleoside analogues and of the strategies that included an early start of treatment with nucleoside analogues as compared to delayed treatment until cirrhosis stage. CC, compensated cirrhosis; CHB, chronic hepatitis B; ETV, entecavir; ICER, incremental cost-effectiveness ratio; TDF, tenofovir disoproxil fumarate.
Figure 2. Tornado diagram showing the results of the one-way sensitivity analysis on the incremental cost-effectiveness ratio of PEG-IFN plus TDF in CC versus TDF in CC.

The base case was €1,152.43/quality-adjusted life year (QALY). CC, compensated cirrhosis; CHB-A, active chronic hepatitis B; DCC, decompensated cirrhosis; LT, liver transplant; PEG-IFN, pegylated interferon; Pr., probability; sCL, clearance of hepatitis B surface antigen; TDF, tenofovir disoproxil fumarate; w tr., with treatment.

Figure 3. Results of the probabilistic sensitivity analysis of PEG-IFN plus TDF in CC versus TDF in CC depicted in the cost-effectiveness plane.

Each one of the 1,000 iterations is represented by a data point. The base case was €1,152.43/quality-adjusted life year (QALY), the incremental outcome was 1.30 QALYs and the incremental cost was €1,496. CC, compensated cirrhosis; PEG-IFN, pegylated interferon; PSA, probabilistic sensitivity analysis; TDF, tenofovir disoproxil fumarate.
acceptability curve. In this case it can be read that for threshold values up to €8,000/QALY, the probability of the strategy PEG-IFN plus TDF in CC being cost-effective (against TDF in CC) was nearly 100%.

**Discussion**

HBeAg-negative CHB is a difficult-to-treat disease particularly in genotype-D-infected patients, who prevail in Italy [6,8]. For this group of patients the current strategy of antiviral therapy is to indefinitely maintain the suppression of HBV replication with oral NAs or to elicit a sustained off-therapy virological control with a finite course of IFN. The sustained suppression or control of viral replication improves quality of life and survival by preventing progression of CHB to cirrhosis, HCC and end-stage liver disease. Response to therapy reduces histological activity and lowers the risks of cirrhosis and HCC, particularly in non-cirrhotic patients. However, starting therapy in the pre-cirrhotic phase of CHB poses the uncertainty of the side effects of long-term treatment and increases total costs. Thus, the preferred therapeutic strategy would be a finite therapy course, intended to achieve a sustained off-treatment control of viral replication with HBsAg loss as the ideal end point. However, HBsAg loss is infrequently achievable with the currently available NAs in HBeAg-negative CHB and the main theoretical advantages of PEG-IFN, including the possibility of sustained virological response off-treatment and immune-mediated control of HBV infection associated with HBsAg loss, and absence of antiviral resistance, are counterbalanced by major disadvantages, such as the low response rate, side effect profile and the need for subcutaneous injections [1]. The evidence that combined HBV DNA and HBsAg serum levels at week 12 provide the early identification of IFN non-responders has garnered much interest in the medical community. We explored the cost-effectiveness of treating treatment-naive HBeAg-negative CHB patients with PEG-IFN as first-line treatment guided by HBV DNA and HBsAg week-12 stopping rule and reserving NAs for second-line sequential treatment in non-responders to PEG-IFN [10,14]. Several cost-effectiveness studies were recently reported [22,26,36–39] assessing different treatments in HBeAg-negative CHB patients and the use of PEG-IFN as first-line treatment followed by NAs was also considered, but only as a secondary option [26]. We proposed the option of early cessation of PEG-IFN after 12 weeks in non-responders with a direct switch to NAs to save time and healthcare resources. This is the first attempt to model the sequential treatment of HBeAg-negative CHB with both PEG-IFN and NAs in a lifetime perspective.

![Figure 4. Results of the probabilistic sensitivity analysis of PEG-IFN plus TDF in CC versus TDF in CC depicted as a cost-effectiveness acceptability curve](image)

The base case was €1,152.43/quality-adjusted life year (QALY). CC, compensated cirrhosis; PEG-IFN, pegylated interferon; TDF, tenofovir disoproxil fumarate.

The results of our study prompt a cost-effective improvement of the management of HBeAg-negative CHB through a shift towards a response-guided multiple drug combination strategy, which is currently the preferred and most effective therapy option in chronic hepatitis C patients [40]. As is common in all model-based cost-effectiveness studies, the main limitations of this study are inherently linked to the use of heterogeneous sources of data and data extrapolations. To this extent, one of the main issues is related to the use in the model of efficacy data obtained from international clinical studies, not specifically focused on genotype D patients, which represent the majority of our target population (Italian CHB patients). However, the largest number of patients of international randomized controlled trials were infected with HBV genotypes B, C and D and the results of the recent validation study on two different cohorts of patients infected with different HBV genotypes showed that week-12 HBsAg stopping rule had 100% specificity in genotype D and 95% in genotype B and C; only one genotype-A-infected patient was missed [14]. In addition, current medical literature provides enough evidence that the early identification of non-responders to PEG-IFN is possible and reliable; moreover current research will allow significant improvements in the near future, possibly identifying genotype-specific HBsAg cutoffs [41]. Data on pharmacological efficacy and effectiveness were extracted from mixed sources of RCTs and long-term follow-up observational studies. Another limitation concerns the population of patients used to derive health utility data, which was not specifically Italian CHB patients (no published study was...
found to report them). Published data from a Spanish pool of CHB patients were instead considered, on the assumption of a commonality of perceived quality of life in the south European region.

Our study provides insights into the economic assessment of treatment strategies for HBeAg-negative CHB, following two main perspectives, the first one assessing the economic efficiency of PEG-IFN as a first-line, the second one exploring the economic efficacy of an early versus delayed treatment with NAs. In the first perspective the adoption of PEG-IFN as a first-line was dominant (that is, more effective and less costly) in all comparisons, with just one exception. Nevertheless, also in this case, where the inclusion of a PEG-IFN first-line resulted in an increased average total cost, the strategy showed a favourable cost-effectiveness profile, with a very low ICER (€1,152/QALY). However, in the two comparisons involving the treatment with antivirals in CHB, the difference in QALY in favour of PEG-IFN first-line was very small, while the difference in absolute survival was slightly in favour of NA-only strategies. For this reason the pharmacoeconomic dominance should be taken with caution, and we believe that the overall result can be interpreted as a substantial equal efficacy, suggesting that the strategies with PEG-IFN as a first-line were yielding the same average effect at a lower cost than those only based on antivirals.

In the second perspective (early versus late treatment in the natural history of CHB) the earlier treatment at a non-cirrhotic stage always resulted in better clinical effectiveness outcomes and higher costs, compared with the option of delaying the therapy until cirrhosis, with ICERs ranging from €11,797/QALY to €20,778/QALY. In Italy, no official threshold has been set to define when a drug can be considered cost-effective. In the absence of a local guidance, one practice frequently adopted in pharmacoeconomic evaluations consists of referring to the non-official rule adopted by the National Institute for Health and Clinical Excellence in the UK, where treatments with an ICER<€30,000/QALY are generally considered cost-effective. Given this threshold, it can be concluded that the early treatment of HBeAg-negative CHB will lead to a more cost-effective outcome than delaying treatment until cirrhosis.

In conclusion, the cost-effectiveness of the management of chronic HBeAg-negative hepatitis B, could be improved significantly by a shift toward a response-guided first-line treatment with PEG-IFN followed by a switch to NAs in non-responders. Given the lack of evidence, we did not consider the possible beneficial effect of lead-in PEG-IFN therapy on the clinical outcome of the patients who will continue treatment with NAs. In most difficult-to-treat patients with chronic hepatitis C, the lead-in treatment with PEG-IFN and ribavirin prior to the addition of new HCV protease inhibitors was proven to be the most cost-effective strategy [40]. The question of whether similar treatment strategies are more effective than monotherapy in chronic HBeAg-negative hepatitis will be answered by the results of the many ongoing clinical trials which address the important issue of combined PEG-IFN and NA therapy.

Disclosure statement
SI, AL and BE are employees of IMS HEOR. Roche Spa, Monza, Italy, supported the development of the model through a service contract with IMS HEOR. FB cooperated with IMS HEOR in the development of the model through a consulting agreement with IMS HEOR. AC and FR are employed by Roche Spa. All other authors declare no competing interests.

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