Liver, Pancreas and Biliary Tract

A cost-effectiveness model to personalize antiviral therapy in naive patients with genotype 1 chronic hepatitis C

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Background and aims: Rapid virologic response is the best predictor of sustained virologic response with dual therapy in genotype-1 chronic hepatitis C, and its evaluation was proposed to tailor triple therapy in F0–F2 patients. Bio-mathematical modelling of viral dynamics during dual therapy has potentially higher accuracy than rapid virologic in the identification of patients who will eventually achieve sustained response. Study’s objective was the cost-effectiveness analysis of a personalized therapy in naive F0–F2 patients with chronic hepatitis C based on a bio-mathematical model (model-guided strategy) rather than on rapid virologic response (guideline-guided strategy).

Methods: A deterministic bio-mathematical model of the infected cell dynamics was validated in a cohort of 135 patients treated with dual therapy. A decision-analytic economic model was then developed to compare model-guided and guideline-guided strategies in the Italian setting.

Results: The outcomes of the cost-effectiveness analysis with model-guided and guideline-guided strategy were 19.1–19.4 and 18.9–19.3 quality-adjusted-life-years. Total per-patient lifetime costs were €25,200–€26,000 with model-guided strategy and €28,800–€29,900 with guideline-guided strategy. When comparing model-guided with guideline-guided strategy the former resulted more effective and less costly.

Conclusions: The adoption of the bio-mathematical predictive criterion has the potential to improve the cost-effectiveness of a personalized therapy for chronic hepatitis C, reserving triple therapy for those patients who really need it.

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1. Introduction

Hepatitis C virus (HCV) infection represents a major global public health problem, with approximately 130 million people infected with chronic hepatitis C (CHC) worldwide [1]. According to the World Health Organization (WHO), an estimated 15 million people live with hepatitis C (2.0% of adults) in the WHO European Region, and hepatitis C causes around 86,000 deaths per year in WHO European Member States [2]. Among the seven known major genotypes of HCV, genotype 1 (G1) is the most prevalent in the USA [3] and Europe [4].

An increasing range of antiviral treatments specific to HCV is currently being made available in clinical practice. Two NS3-NS4 HCV protease inhibitors, telaprevir (TVR) and boceprevir (BOC), indicated in the treatment of G1 HCV in combination with peg-interferon-alpha and ribavirin, were introduced only a few years ago. Sofosbuvir (SOF) and simeprevir (SIM) are already available in the US and EU markets, while a new range of products that will not need to be used in combination with interferon are expected to become available within the next 6–12 months. In spite of the high efficacy and optimal safety profile, the cost associated with these treatments, with the potential impact on the budget of national healthcare systems in Europe represents a major concern. This consideration highlights the necessity to identify personalized treatment patterns, which may vary between countries with different economical constraints [5], allowing the optimization of clinical outcomes along with economic impact.
Randomized clinical trials (RCTs) have shown that triple therapy (TT) with peg-interferon-alpha, ribavirin, and BOC or TVR increases the rates of sustained virologic response (SVR) of about 25–30% as compared to dual therapy (DT) in G1 treatment-naive CHC patients [6–9]. However, to optimize the clinical outcome along with the risk–benefit profile and overall cost, Italian clinical guidelines suggest to use TT as the first line treatment in patients with advanced fibrosis (METAVIR fibrosis scores F3–F4), and to adopt TT only in F0–F2 patients who are not likely to achieve SVR with DT [10] according to the main on treatment predictor of SVR, that is the achievement of undetectable HCV-RNA after 4 weeks of dual therapy (rapid virologic response, RVR). However, RVR is only observed in about one-third of CHC-G1 patients who achieve an SVR [11], while the remaining patients, because of a slower block of viral replication, show longer viral clearance kinetics. An alternative measure to identify patients with a high chance of SVR when treated with DT can be the application of a bio-mathematical model of viral dynamics during the first month of DT. Bio-mathematical modeling of HCV-RNA and alanine aminotransferase (ALT) decline during peg-IFN/RBV therapy has already been shown to be able to predict SVR with high accuracy in both rapid and slow responders [12].

The objective of the current study was twofold: (1) to analyse the performance of a simplified version of the original bio-mathematical model by Colombatto et al. [13] in predicting SVR in HCV G1 patients, using only two ALT measures, at week 1 and 2, in addition to ALT and HCV-RNA measures at baseline and week 4 (and 2) to observe the predicted prediction power to inform a decision-analytic model for a cost-effectiveness analysis of personalized anti-HCV therapy in an Italian setting in treatment-naive F0–F2 patients.

2. Materials and methods

2.1. The bio-mathematical model

Viral and infected cell dynamics can be analysed at the single-patient level by bio-mathematical modelling, using both HCV-RNA and ALT declines during the first month of therapy, as previously described elsewhere [13] and here summarized in Supplementary Materials.

In the present study, we compared the standard approach where the parameters of viral dynamics are computed using the full data set of ALT and HCV-RNA (baseline, day 2–4–7–14 and 28) with a simplified one, where we used for the same patient only the ALT measured at baseline, day 7–14 and 28 and HCV-RNA measured at baseline and day 28 (week 4), as required by standard management of antiviral therapy. Accordingly, in the latter the value of the baseline infected cell clearance rate \( \theta \) was obtained by the least square fit of ALT levels measured at the times \( t \) = 0, 7, 14, and 28 days, using the equation \( \ln(\text{ALT}(t) - \text{ALT}_0)/(\text{ALT}_0 - \text{ALT}_T)/t \), where \( \text{ALT}_T \) is the extrapolated normal value of ALT in that patient. Another difference in the simplified model was that without the value of HCV-RNA measured at day 2, the antiviral effectiveness in the first phase \( \epsilon \) could not be measured. As a consequence, the direct antiviral effects of the therapy were not separated in 2 phases, but assessed as a whole assuming \( \epsilon = 0 \) and computing at week 4 the residual average viral production \( 1 - \epsilon \) \( \gamma \) \( \Psi_0 \), where \( \gamma \) is the asymptotic viral production coefficient and \( \Psi_0 \) is the baseline viral production rate.

2.2. Validation in observed patients

The standard and simplified modelling approaches were applied to 150 consecutive G1 patients (mean age 49.9 years, 76% males, 57% treatment-naive, 47% F0–F2, 17% subtype 1a), who received standard duration treatments (101 patients) with peg-interferon and ribavirin or (49 patients) model-tailored durations (EudraCT: 2006-002483-26). The Ethical Committee of the Hospital approved the above studies and the patients signed a written informed consent.

2.3. Design of the decision-analytic model

A decision-analytic model was developed in Microsoft Excel 2011 (Microsoft, Redmond, WA) to inform the cost-effectiveness analysis of personalized anti-HCV therapy. The analysis was carried out from the perspective of the Italian national healthcare system and with a lifetime time horizon. A 3.5% discount rate was applied both to outcomes and costs. Estimated outcomes were life-years (LYs) and quality-adjusted life-years (QALYs) gained.

Two strategies were compared: guideline-guided (GG) and model-guided (MG). For each strategy two situations were considered, with TT including the addition of either BOC or TVR to peg-interferon and ribavirin. In total, therefore, four strategies were compared: GG-BOC, GG-TV, MG-BOC and MG-TV. All simulated G1, F0–F2, treatment-naive patients received DT for four weeks (lead-in period) and the two strategies then differed in the criterion applied to identify those who could continue DT rather than switching to TT (RVR and bio-mathematical model test for GG and MG strategies, respectively). RVR was defined as not detectable HCV RNA levels at week 4, while the model test was defined by a threshold of residual infected cells and free virions at the end of therapy, as computed at week 4 by a decline in ALT (week 1, 2 and 4) and HCV-RNA levels (week 4).

The decision-analytic model was designed with a mixed technique: a decision tree for the initial treatment period (28–96 weeks) followed by a long-term Markov model to simulate the patients’ remaining lifetime. The decision tree simulated the adoption of the GG or MG strategy, using RVR or the model test, respectively, to identify the proportion of patients suitable to continue DT rather than adding BOC or TVR. The initial characteristics and distribution of fibrosis of the simulated population was derived from observed data in the validation cohort. Given the short time frame of the decision tree module, it was assumed that the level of fibrosis did not change in simulated patients during this first stage. All input data used in the economic model are reported in Supplementary Table S1.

2.4. Decision tree for initial treatment

A description and schematic representation of the decision trees are presented as Supplementary materials to this article (Figs. S1–S4). In general, after the initial four-week lead-in with DT, patients were tested for RVR (GG strategy) or with the bio-mathematical model (MG strategy). The rates of RVR and positive model tests were obtained from the observed validation cohort. These patients were simulated to continue DT for another 44 weeks and the final SVR rates were, again, derived from observed data in the validation cohort. Patients not achieving SVR were treated differently according to their stage of fibrosis. F0 and F1 patients were assumed not to be retreated, while F2 patients were retreated with specific protocols derived from the RESPOND-2 study [14] and the REALIZE study [15] for BOC and TVR, respectively.

Patients not achieving RVR or a positive model test after the initial lead-in with DT were switched to TT. The response-guided protocol reported in the SPRINT-2 study [8] for BOC and the ADVANCE study [6] for TVR was followed.

Overall, the duration of the first part of the simulation defined by the decision tree was of 28, 48, 52 or 96 weeks, depending on the specific treatment pattern.
According to the observed data in the validation cohort the biomathematical model was non-satisfactorily applicable to 9.9% of the observed patients. We, thus, assumed that while evaluating the MG strategies, 90.1% of the cohort was actually treated with these, while 9.9% was treated with the corresponding GG strategies.

2.5. Long-term Markov model

The Markov model (Fig. 1) allowed the estimation of long-term costs, survival and QALYs as a function of the proportion of patients achieving SVR at the end of the initial treatment period. Health states represent disease progression from compensated to decompensated cirrhosis, hepatocellular carcinoma, liver transplant and death (Fig. 1). Transition probabilities between health states were derived from the published literature describing the course of the disease or validated assumptions in previously published economic models (Supplementary Table S1). Health state utilities were derived from a previous Italian cost-effectiveness analysis in CHC (Supplementary Table S1). Given the perspective of the Italian national healthcare system adopted, only direct medical costs were considered; these consisted of drug costs, costs for strategy-related tests (at week 4) and costs to manage the long-term course of the disease. Drug costs were calculated on the basis of recommended doses and ex-manufacturer prices. The calculated cost of DT was based on a 73.4% share of peg-interferon alpha-2a of the total (alpha-2a plus alpha-2b) use in chronic hepatitis B (Italian market share data, January 2014). To calculate the average dose of ribavirin and peg-interferon alpha-2b, the average body weight

Fig. 1. Schematic representation of the long-term Markov model. Death probability for all causes is considered (not shown). F0–F4, METAVIR fibrosis; SVR, sustained virologic response; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; post LT, post liver transplantation.

Fig. 2. The best prediction of sustained virologic response in the 64 patients with a lower fibrosis stage (METAVIR F0–2) was obtained using the threshold level given by the product of infected cells and free virions at the end of therapy equal to 400. SVR, sustained virologic response; eot, end of therapy; I, infected cells; V, free virions.
Table 1
Predictive performance of the index given by the product of infected cells and free virions at the end of therapy, compared with that of rapid virologic response, in the whole cohort and in the subgroup of F0–2 patients.

<table>
<thead>
<tr>
<th></th>
<th>SVR</th>
<th>No SVR</th>
<th>Total</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>DA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V^*_{\text{tot}} &lt; 400$</td>
<td>57</td>
<td>5</td>
<td>62</td>
<td>87.7%</td>
<td>92.9%</td>
<td>91.9%</td>
<td>89.0%</td>
<td>90.4%</td>
</tr>
<tr>
<td>$V^*_{\text{tot}} &gt; 400$</td>
<td>8</td>
<td>65</td>
<td>73</td>
<td>40.0%</td>
<td>97.1%</td>
<td>92.9%</td>
<td>63.6%</td>
<td>69.6%</td>
</tr>
<tr>
<td>RVR yes</td>
<td>26</td>
<td>2</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVR no</td>
<td>39</td>
<td>68</td>
<td>107</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>F0–2 patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V^*_{\text{tot}} &lt; 400$</td>
<td>30</td>
<td>2</td>
<td>32</td>
<td>88.2%</td>
<td>93.3%</td>
<td>93.8%</td>
<td>87.5%</td>
<td>90.6%</td>
</tr>
<tr>
<td>$V^*_{\text{tot}} &gt; 400$</td>
<td>4</td>
<td>28</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVR yes</td>
<td>20</td>
<td>2</td>
<td>22</td>
<td>58.8%</td>
<td>93.3%</td>
<td>90.9%</td>
<td>66.7%</td>
<td>75.0%</td>
</tr>
<tr>
<td>RVR no</td>
<td>14</td>
<td>28</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DA, diagnostic accuracy; eot, end of therapy; I, infected cells; NPV, negative predictive value; PPV, positive predictive value; RVR, rapid virologic response; Sens, sensitivity; Spec, specificity; SVR, sustained virologic response; V, free virions.

reported in the study by Asicone et al. was considered (average: 69.9 kg; in 66.9% of the cases the body weight was below 75 kg) [16].

Disease management costs associated with the progression of CHC were based on a set of annual costs (including hospitalizations, specialized activities and diagnostic activities) related to the different severity stages of chronic hepatitis B and C, as reported in a publication from the Associazione Italiana per lo Studio del Fegato (AISF) [17].

3. Results

3.1. Bio–mathematical model

Successful fitting of the ALT decline, required for model simulations, was obtained in 135 of 150 (90%) patients. The reason for non fitting in the remaining 15 patients was the ALT increase at day 7 and 14, which was observed more often in partial or no responder patients (10), than in relapsers (3) or SVR (2) patients. The main clinical characteristics, therapy response and outcomes in the cohort and in the subgroup of 64 patients with a lower fibrosis stage (METAVIR stage F0–F2) are shown in Supplementary Table S2.

As previously reported [12], the model-computed parameters that best predict therapy outcome (SVR versus no SVR) are the estimates of end-of-therapy infected cells and viral load. Using the full data set of ALT and HCV-RNA in the whole cohort of CHC-G1 patients the model computed end of therapy (eot) infected cells ($I_{\text{eot}}$) and free virions ($V_{\text{eot}}$) showed lower accuracy in the prediction of SVR as compared to their product ($V^*_{\text{eot}}$): AUROC $I_{\text{eot}} = 0.906$, AUROC $V_{\text{eot}} = 0.930$, AUROC $V^*_{\text{eot}} = 0.941$. The $V^*_{\text{eot}}$ index obtained using all data (ALT and HCV-RNA at day 0–2–4–7–14–21–28) or using the simplified data set (ALT at day 0–7–14–28 and HCV-RNA at day 0–28) showed a very high correlation ($R = 0.94$). The best prediction of SVR in the 64 patients with METAVIR stage F0–2 fibrosis was obtained using the threshold level of $V^*_{\text{eot}} = 400$ (Fig. 2), that identified SVR with 93.8% PPV and 88.2% sensitivity. The predictive performance of the $V^*_{\text{eot}} = 400$ index compared with that of achieving RVR, in the whole cohort and the subgroup of F0–2 patients, is reported in Table 1.

3.2. Decision-analytic model

In the base case analysis, the four strategies provided similar clinical outcomes: 20.06–20.20 discounted Lys and 18.91–19.42 discounted QALYs (Table 2). The total average per-patient lifetime costs were €28,800 and €29,900 with GG-BOC and GG-TV, and €25,200 and €26,000 with MG-BOC and MG-TV.

The cost-effectiveness analysis was primarily performed in terms of cost per QALY gained to compare the MG and GG strategies (keeping the choice of the protease inhibitor fixed). When comparing the MG and GG strategies, either with BOC or TVR, the former was marginally more effective and less costly; that is, dominant according to the pharmaco-economic definition (Table 3).

3.3. Sensitivity analysis

Both one-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were performed for all possible comparison. The case of the MG-TV versus GG-TV comparison is presented. TVR was the protease inhibitor selected, because of the favourable ICER demonstrated when compared with BOC for both the MG and GG strategies (Table 3).

DSA was performed, varying one model parameter at a time in the range ±10% of its base case value and assessing its impact on the net monetary benefit (NMB), which, assuming a willingness-to-pay threshold of €30,000/QALY, in the base case was €8802. In Fig. 3, results of the DSA are presented as a tornado diagram, depicting the first 15 parameters that caused the NMB to vary the most, when assuming the lower and upper values of their ranges. The model appeared to be most sensitive to variations in the proportions of SVR at the end of the 48-week course of DT in both strategies.

The PSA was conducted by assigning to each model's parameter a probabilistic distribution to describe its uncertainty. Where the uncertainty was not available from original sources the standard deviation of 10% of the base case was assumed. The result of the PSA, calculated with 1000 iterations, is presented as a scatter plot in the cost-effectiveness plane in Supplementary Fig. S5. In 4.2% of the cases, the points fell in the northwest quadrant, meaning

Table 2
Base case outcomes of the four analysed strategies.

<table>
<thead>
<tr>
<th></th>
<th>Disc Lys</th>
<th>Disc QALYs</th>
<th>Disc costs (Euro)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG-BOC</td>
<td>20.06</td>
<td>18.91</td>
<td>28,773</td>
</tr>
<tr>
<td>GG-TV</td>
<td>20.20</td>
<td>19.28</td>
<td>29,861</td>
</tr>
<tr>
<td>MG-BOC</td>
<td>20.09</td>
<td>19.14</td>
<td>25,154</td>
</tr>
<tr>
<td>MG-TV</td>
<td>20.20</td>
<td>19.42</td>
<td>26,021</td>
</tr>
</tbody>
</table>

BOC, boceprevir; Disc, discounted; GG, guideline-guided (strategy); Lys, life-years; MG, model-guided (strategy); QALYs, quality-adjusted life-years; TVR, telaprevir.

Table 3
Incremental and cost-effectiveness analysis for base case results.

<table>
<thead>
<tr>
<th></th>
<th>Disc QALYs</th>
<th>Disc costs (€)</th>
<th>ICER (€/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MG-TV vs GG-TV</td>
<td>0.14</td>
<td>−3839</td>
<td>Dominant</td>
</tr>
<tr>
<td>MG-BOC vs GG-BOC</td>
<td>0.23</td>
<td>−3618</td>
<td></td>
</tr>
<tr>
<td>MG-TV vs MG-BOC</td>
<td>0.29</td>
<td>867</td>
<td>3035</td>
</tr>
<tr>
<td>GG-TV vs GG-BOC</td>
<td>0.37</td>
<td>1088</td>
<td>2936</td>
</tr>
</tbody>
</table>

BOC, boceprevir; Disc, discounted; GG, guideline-guided (strategy); ICER, incremental cost-effectiveness ratio; MG, model-guided (strategy); QALYs, quality-adjusted life-years; TVR, telaprevir.
that MG-TVR was less effective and more costly than GG-TVR (that is, MG-TVR is dominated). In none of the cases, points fell in the northeast quadrant (which would have meant that MG-TVR was more effective and more costly than GG-TVR). The remaining cases were related to MG-TVR being less costly than GG-TVR. In 85.0% of the cases, points fell in the southeast quadrant, meaning that MG-TVR is dominant (as in the base case result). In the remaining 10.8% of the cases, points fell in the southwest quadrant. In conclusion, the PSA showed that, when introducing variations in all model parameters, the result of MG-TVR being dominant compared with GG-TVR is confirmed with a high probability.

4. Discussion

In this study, we assessed and compared the cost-effectiveness of two different approaches to individualized therapy, where triple therapy with BOC and TVR is given only to F0–F2, CHC with limited probability of response to dual therapy. One approach was the traditional RVR-based strategy (GG), exploiting the power of statistical data from clinical trials and the evidence of a higher probability of response of patients with RVR. The second strategy (MG) was the systems medicine approach of clinical decision-making guided by the deterministic evidence provided by a bio-mathematical model, which simulates the virus and infected cell dynamics during treatment.

The decision-analytic model allowed the cost-effectiveness comparison of the different strategies, both in terms of clinical outcomes (QALYs) and overall per-patient lifetime costs. The total average per-patient lifetime costs were €28,800 and €29,900 with GG-BOC and GG-TVR, and €25,200 and €26,000 with MG-BOC and MG-TVR. When comparing the MG and GG strategies, using either BOC or TVR, the former was more effective and less costly and, thus, dominant according to the pharmacoeconomic definition.

The results of our study, therefore, demonstrate that the new model-guided algorithm for personalized antiviral therapy was dominant; that is, more effective and less costly, leading to a saving of €3600–3900 per patient in terms of lifetime costs. The sensitivity analysis tested the robustness of the conclusion under a wide range of variations of considered parameters. Overall, it appears that the proposed algorithm has the potential to produce a significant saving in healthcare financial resources with the same quality outcomes as the standard RVR-based approach. However, it should be clarified the treatment approaches analysed in this study (especially triple therapy with first generation DAAs) are already out-dated, given the rapidly evolving clinical landscape for HCV treatments. As a consequence, the aim of the current paper is to proof the theoretical concept of the systems medicine approach guided by the deterministic evidence of a bio-mathematical model mixed with the predictive power of a health economics model to inform health policy decision-making.

One important limitation of the bio-mathematical model is that a successful fitting of the ALT decline, required for model simulations, was obtained in about 90% of patients, so the model was not applicable in about 10% of the cases. In terms of cost-effectiveness analysis this was addressed considering that, while evaluating the model-guided strategy, 90% of the cohort was actually treated with this algorithm, while 10% was treated with the standard RVR-based approach.

As is common with health economic analyses based on decision-analytic models, the study presents several limitations. The CHC therapeutic area is, however, well represented in the international health economic literature. A range of model-based analyses in CHC in an Italian and an international setting were analysed and we feel that the decision-analytic model in this study is well in line with most of the previous examples, both in terms of design and input data [19–24].

In conclusion, the adoption of a systems medicine approach to individualized antiviral therapy in treatment-naïve CHC patients,
substituting the standard probabilistic criterion with deterministic bio-mathematical modelling of the virus and infected cell dynamics, has the potential to improve the effectiveness of anti-HCV therapy in the individual patient. The new algorithm allows a more accurate identification of patients who can be effectively treated with DT, so that high-cost new antiviral drugs can be reserved for those who really need them. The cost–effectiveness analysis of this MG strategy, compared with the GC strategy, demonstrates that its adoption would provide benefit, both in terms of clinical outcomes and cost containment.

Conflict of interest
The production of this manuscript was supported by an unconditional research grant from Roche Spa, Monza, Italy. S. Iannazzo was health economics consultant in several therapeutic areas in the last 6 months for Roche, Amgen, Ariad Pharmaceuticals, Biogen Idec, Novartis Farma. Piero Colombatto in the last 6 months took part in advisory boards for Janssen and Abbvie. The other authors do not have conflict of interest to disclose.

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Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2014.12.008.

References