INTRODUCTION

- An increasing range of antiviral treatments specific to chronic hepatitis C (CHC) is currently being made available in clinical practice. Two NS3/4A HCV protease inhibitors, telaprevir (TVR) and boceprevir (BOC), indicated in the treatment of genotype 1 (G1) HCV in combination with peg-interferon alpha and ribavirin, (dual therapy – DT), were introduced only a few years ago. Sofosbuvir and simeprevir are already available in the US and EU markets, while a new range of products that will not be used in combination with interferon are expected to become shortly available.

- 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.

- Triple therapy (TT) with peg-interferon alpha, ribavirin, and BOC or TVR increases the rates of sustained virologic response (SVR) as compared to DT in GT1 treatment-naive CHC patients.

- To optimize clinical outcomes along with overall cost, Italian clinical guidelines suggest to use TT as the first line treatment in patients with advanced fibrosis (METAIVIR fibrosis scores F3-F4), and to adopt DT only in F0-F2 patients who are not likely to achieve SVR with DT (1) according to the main on treatment predictor of SVR, that is the achievement of undetectable HCV-RNA after 4 weeks of DT (rapid virologic response, RVR).

- An alternative measure to identify patients with a high chance of SVR can be the application of a bio-mathematical model of viral dynamics. Bio-mathematical modelling of HCV-RNA and alamine aminotransferase (ALT) decline during DT has already been shown to be able to predict SVR with high accuracy (2).

OBJECTIVE

- The objective of the current study was to use a simplified version of the bio-mathematical model developed by Colombo et al. (3) 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.

METHODS

- The simplified version of the bio-mathematical model allows the prediction of SVR in HCV G1 patients, using only two ALT measures, at week 2 and 4, in addition to ALT and HCV-RNA measures at baseline and week 4 necessary for RVR. This was validated in a cohort of 150 consecutive G1 CHC patients treated with DT at the University Hospital in Pisa, Italy.

- A decision-analytic model was developed in Microsoft Excel 2011 in the perspective of the Italian National Healthcare System with a lifetime horizon time. A 3.5% discount rate was applied both to outcomes and costs.

- Two strategies were compared: guideline-guided (GG) and model-guided (MG). All simulated patients received DT for four weeks and the two strategies then differed in the criterion applied to identify those who could continue DT rather than switching to TT (RVR criterion or bio-mathematical model test). RVR was defined as not detectable HCV-RNA levels at week 4, while the model test was defined by a threshold in the 150 consecutive selected patients and free viremia at the end of therapy, as computed by week 4 by a decline in ALT (week 1, 2, 4 and ALT) and HCV-RNA levels (week 4).

RESULTS

- Decision tree
  - After the initial four-week lead-in with DT, patients were tested for RVR (GG strategies) or with the bio-mathematical model test (MG strategies). The rates of RVR and positive model test were obtained from the observed validation cohort.
  - Patients with RVR or positive model test were simulated to continue DT for another 4 weeks and the final SVR rates were based on observed data in the validation cohort.
  - Patients not achieving SVR if F0 and F1 were assumed not to be retreated, if F2 were assumed to be retreated with specific protocols derived from RESPONSE-2 (4) and REALIZE (1).
  - 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 SPXINT-7 (6) for BOC and in ADVANCE (7) for TVR was followed.

- Long-term Markov model
  - Transition probabilities and health state utilities in the Markov model were derived from published clinical literature describing the course of the disease or from previously published economic models (9-12, 13).
  - Costs included, drugs, strategy-related tests (based on current prices and tariffs) and the management of the long-term outcomes of the disease (i.e., liver transplantation).
  - The rates of RVR and positive model test were simulated to continue DT for another 4 weeks and the final SVR rates were based on observed data in the validation cohort.
  - Patients not achieving SVR if F0 and F1 were assumed not to be retreated, if F2 were assumed to be retreated with specific protocols derived from RESPONSE-2 (4) and REALIZE (1).
  - 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 SPXINT-7 (6) for BOC and in ADVANCE (7) for TVR was followed.

CONCLUSIONS

- The adoption of a SVR predictive criterion based on a bio-mathematical model, has the potential to improve the cost-effectiveness of a personalized anti-HCV therapy, allowing a more accurate identification of patients who can be effectively treated with DT and reserving high-cost BOC- and TVR-based TT for those who really need it.

REFERENCES

- The PSA was conducted with 1,000 iterations. In 4.2% of the cases, the points fell in the NE quadrant, meaning that MG-TV was less effective and more costly than GG-TV. In none of the cases, points fell in the SE quadrant, meaning that MG-TV is dominant (as in the base case result). In the remaining 10.8% of the cases, points fell in the SW quadrant. In conclusion, the PSA showed that the result of MG TV being dominant compared with GG-TV is confirmed with a high probability.