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Modeling Cost-Effectiveness and Health Gains of a "Universal" Versus "Prioritized" Hepatitis C Virus Treatment Policy in a Real-Life Cohort

Loreta A. Kondili,[1] Federica Romano,[2] Francesca Romana Rolli,[2] Matteo Ruggeri,[2] Stefano Rosato,[1] Maurizia Rossana Brunetto,[3] Anna Linda Zignego,[4] Alessia Ciancio,[5] Alfredo Di Leo,[6] Giovanni Raimondo,[7] Carlo Ferrari,[8] Gloria Taliani,[9] Guglielmo Borgia,[10] Teresa Antonia Santantonio,[11] Pierluigi Blanc,[12] Giovanni Battista Gaeta,[13] Antonio Gasbarrini,[2] Luchino Chessa,[14] Elke Maria Erne,[15] Erica Villa,[16] Donatella Ieluzzi,[17] Francesco Paolo Russo,[15] Pietro Andreone,[18] Maria Vinci,[19] Carmine Coppola,[20] Liliana Chemello,[15] Salvatore Madonia,[21] Gabriella Verucchi,[18] Marcello Persico,[22] Massimo Zuin,[23] Massimo Puoti,[19] Alfredo Alberti,[15] Gerardo Nardone,[13] Marco Massari,[24] Giuseppe Montalto,[25] Giuseppe Foti,[26] Maria Grazia Rumi,[23] Maria Giovanna Quaranta,[1] Americo Cicchetti,[2] Antonio Craxì,[25] and Stefano Vella,[1] on behalf of the PITER Collaborating Group*

We evaluated the cost-effectiveness of two alternative direct-acting antiviral (DAA) treatment policies in a real-life cohort of hepatitis C virus–infected patients: policy 1, "universal," treat all patients, regardless of fibrosis stage; policy 2, treat only "prioritized" patients, delay treatment of the remaining patients until reaching stage F3. A liver disease progression Markov model, which used a lifetime horizon and health care system perspective, was applied to the PITER cohort (representative of Italian hepatitis C virus–infected patients in care). Specifically, 8,125 patients naive to DAA treatment, without clinical, sociodemographic, or insurance restrictions, were used to evaluate the policies' cost-effectiveness. The patients' age and fibrosis stage, assumed DAA treatment cost of €15,000/patient, and the Italian liver disease costs were used to evaluate quality-adjusted life-years (QALY) and incremental cost-effectiveness ratios (ICER) of policy 1 versus policy 2. To generalize the results, a European scenario analysis was performed, resampling the study population, using the mean European country-specific health states costs and mean treatment cost of €30,000. For the Italian base-case analysis, the cost-effective ICER obtained using policy 1 was €8,775/QALY. ICERs remained cost-effective in 94%-97% of the 10,000 probabilistic simulations. For the European treatment scenario the ICER obtained using policy 1 was €19,541.75/QALY. ICER was sensitive to variations in DAA costs, in the utility value of patients in fibrosis stages F0-F3 post–sustained virological response, and in the transition probabilities from F0 to F3. The ICERs decrease with decreasing DAA prices, becoming cost-saving for the base price (€15,000) discounts of at least 75% applied in patients with F0-F2 fibrosis. *Conclusion*: Extending hepatitis C virus treatment to patients in any fibrosis stage improves health outcomes and is cost-effective; cost-effectiveness significantly increases when lowering treatment prices in early fibrosis stages. (HEPATOLOGY 2017;66:1814-1825)

Hepatitis C virus (HCV) chronic infection is a worldwide public health concern because it is one of the leading causes of cirrhosis, hepatocellular carcinoma (HCC), and liver transplantations worldwide. An estimated 71 million people have chronic hepatitis C infection, and a significant number of those who are chronically infected will develop cirrhosis or liver cancer. Approximately 399,000 people die each year from hepatitis C, mostly from cirrhosis and HCC.[1,2]

Although the overall prevalence of HCV infection has been declining and the incidence has dropped significantly since peaking in 1989, the total health care costs for treating infected individuals have continued to rise.[3]

Abbreviations: DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; IFN, interferon; QALY, quality-adjusted life-years; SVR, sustained virological response; WTP, willingness to pay.

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Given the enormous health loss attributable to viral hepatitis and the availability of effective treatment, there exists a great opportunity to drastically improve public health.[4] The development of direct-acting antiviral agents (DAAs) represents a historical breakthrough, in that their use can eradicate HCV in >95% of infected individuals, preventing chronic liver disease from developing into cirrhosis and HCC.[5-7] In light of this, arresting or preventing the onset of severe liver disease has become a reality and thus a critical focus of treatment. However, enthusiasm for the new drugs has been dampened by the initially exorbitant price and the great number of persons who would need these drugs, making their sustained use unfeasible for health care systems, particularly in resource-constrained countries. This has given rise to a heated debate as to how to best prioritize patients for treatment, yet the optimal timing of treatment and the real-life added health benefits and costs of early treatment remain unknown.[8,9] Since 2015, DAA treatment has been recommended for patients with chronic HCV liver disease, with the exception of those with a short life expectancy not related to liver disease.[10,11] However, currently, most insurers cover therapy only in the advanced stages of fibrosis.

Given that a "life without HCV" is now an attainable goal, it is crucial that health policies that include the cost-effectiveness of access to treatment for patients with chronic HCV in care be developed. To this end, we evaluated the health gains and costs of two strategies that differed in terms of the start times of DAA interferon (IFN)–free regimens. The evaluation was performed using a lifetime multicohort model of real-life patients with chronic HCV infection considered to be representative of patients in care.[12]

Patients and Methods

SCENARIOS OF TREATMENT POLICY

Two scenarios of policies for DAA IFN-free regimens were simulated and compared:

*Available from: https://www.progettopiter.it/rete.aspx.

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ARTICLE INFORMATION:

From the [1]Istituto Superiore di Sanità, Rome, Italy; [2]Catholic University, Rome, Italy; [3]University of Pisa, Pisa, Italy; [4]University of Florence, Florence, Italy; [5]University of Turin, Turin, Italy; [6]University of Bari, Bari, Italy; [7]University Hospital of Messina, Messina, Italy; [8]Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; [9]Sapienza University of Rome, Rome, Italy; [10]University of Naples Federico II, Naples, Italy; [11]University of Foggia, Foggia, Italy; [12]Ospedale Santa Maria Annunziata, Florence, Italy; [13]Second University of Naples, Naples, Italy; [14]University of Cagliari, Cagliari, Italy; [15]University of Padua, Padua, Italy; [16]University of Modena and Reggio Emilia, Modena, Italy; [17]Azienda Ospedaliero Universitaria di Verona, Verona, Italy; [18]University of Bologna, Bologna, Italy; [19]Niguarda Ca' Granda Hospital, Milan, Italy; [20]Gragnano Hospital, Naples, Italy; [21]Cervello Hospital, Palermo, Italy; [22]University of Salerno, Salerno, Italy; [23]University of Milan, Milan, Italy; [24]IRCSS-Azienda Ospedaliera Santa Maria Nuova, Reggio Emilia, Italy; [25]University of Palermo, Palermo, Italy; [26]Bianchi Melacrino-Morelli Hospital, Reggio Calabria, Italy.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Loreta A. Kondili, M.D., Ph.D.
National Center for Global Health, Istituto Superiore di Sanità
Viale Regina Elena 299
00161 Rome, Italy
E-mail: loreta.kondili@iss.it
Tel: + 39-06-4990-3813

1. Policy 1: "universal," treat all patients, independently of the fibrosis stage
2. Policy 2: treat only "prioritized" patients and delay treatment of the remaining patients until reaching fibrosis stage F3

A description of the data-source analysis and modeling, in addition to that provided below, can be found in the Supporting Information.

STUDY DESIGN

The analysis followed two steps: we first computed the cost-effectiveness ratio associated with the population of PITER,[12] then applied a resampling procedure to generalize the PITER Italian population to different European countries. We associated to this population the average costs of disease stages of five European countries to obtain an incremental cost-effectiveness ratio (ICER) that is representative of a European context.

STUDY POPULATION

The ongoing Italian HCV cohort (PITER) of 8,125 consecutive patients undergoing care for chronic HCV infection in approximately 100 public clinical centers in the period from May 2014 to December 2015 was considered (Supporting Tables S2 and S3).[12]

MODEL STRUCTURE

Lifetime HCV disease progression during the natural history of chronic infection and the related costs were evaluated using an adapted multicohort Markov model in a lifetime horizon and health care system perspective (Fig. 1).[13,14] Patients entered the model at the proper age and fibrosis stage (i.e., stages F0, F1/2, F3, and F4 or in the stages of decompensated cirrhosis and/or HCC), and they were followed inside the model over a lifetime. The model inputs are shown in Tables 1 and 2.[15-18]

TRANSITION PROBABILITIES

Progression of HCV liver disease was considered as an increase in the severity of liver fibrosis (from F0 to F4 according to the Metavir classification). In the base-case analysis, the transition probabilities from fibrosis stages F0 to F4 was assumed to be linear over time, following a constant annual progression rate. Patients could remain in their current stage or deteriorate; possible regression of liver fibrosis following viral eradication was not taken into consideration. Patients who did not reach a sustained virological response (SVR) were assumed to have proceeded through the natural history of liver disease and to have not been retreated. Patients with mild fibrosis who achieved SVR were considered to have had no risk of further liver disease progression; the reinfection rate was not considered. It was possible for patients with cirrhosis to progress to decompensated cirrhosis or HCC, which were considered in the model to be mutually exclusive. The stage of decompensated cirrhosis or HCC could have led to the patient's being selected for an orthotopic liver transplantation. Given that transplant costs are relatively high, the model envisaged two separate statuses: one for the first year after the transplant and one for the successive years. Finally, patients in these two stages could have progressed toward death. Each patient was assumed to have progressed annually through the various stages of fibrosis according to the natural disease progression rate, considering also the SVR, for the two HCV treatment scenarios. Based on the transition probabilities, each patient could follow one of three different paths in each life-year cycle: (1) continue in the same health without suffering from any event, (2) have a liver-related event, or (3) die of a liver-related cause (Fig. 1). In patients with cirrhosis, the residual risks for HCC and slower disease progression compared to patients who achieved SVR prior to reaching cirrhosis were considered.[19-22] In patients who achieved SVR in the cirrhosis stage, the residual risks for HCC and slower disease progression compared to patients who achieved SVR prior to reaching cirrhosis were calculated using the disease progression based on the SVR ratios reported for patients with a fibrosis stage higher than F3 (Tables 1 and 2). The transition probabilities for patients who achieved SVR in the stage of decompensated cirrhosis or HCC were assumed to be the same as in patients who did not achieve SVR. Although these assumptions are potential limitations of the study, they are conservative as they are actually detrimental to the policy under consideration.

In the sensitivity analysis, transition probabilities and nonliver mortality rates were assumed to follow a nonlinear progression. To model this assumption, an exponential distribution was associated with each transition probability.

Patients coinfected with human immunodeficiency virus (3% of the cohort) were considered to have had the same HCV transition probabilities as the HCV

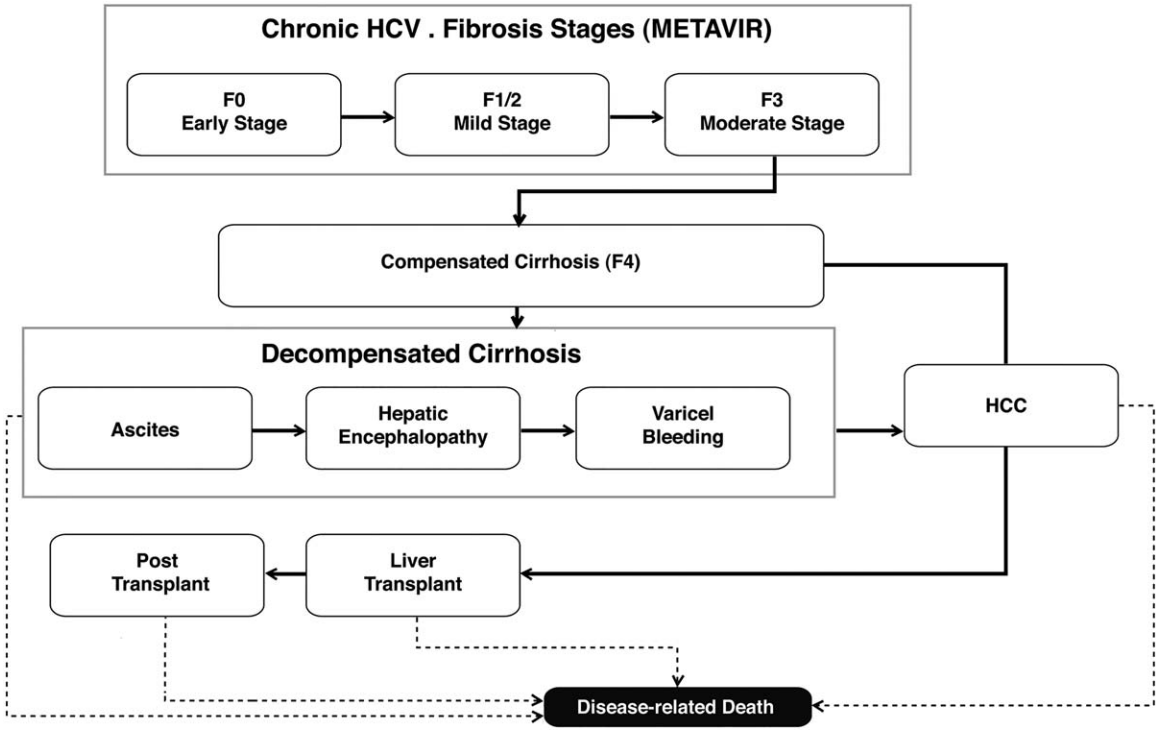

FIG. 1. Markov model of progression of HCV-related liver disease. Potential outcomes of chronic liver disease progression are defined as specific health states reported in each of the boxes. In the Markov chain, each real-life patient moves through states as indicated by the arrows. The arrow indicates the transition from one state to the other according to the natural history of chronic liver disease. Specifically, in this Markov modeling process for patients with cirrhosis, it was possible to progress to four stages: three stages of decompensated cirrhosis (i.e., encephalopathy, ascites, or variceal bleeding) and HCC, which were considered in the model to be mutually exclusive.

monoinfected patients; this assumption would not have affected the results, given that the coinfected patients were included in the planning strategies in the same way (i.e., prioritized independently of the fibrosis stage).

EFFICACY: SVR RATES

IFN-free HCV regimens of second-generation DAAs, approved by the US Food and Drug Administration and the European Medicines Agency, were considered. The likelihood of an SVR was defined in accordance with the SVR rates of IFN-free treatment regimens, recommended as preferred or alternative treatments for each HCV genotype (stratified by presence or absence of cirrhosis) in the guidelines of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases and validated by expert clinicians.[10,11] The SVR and the standard errors used in the base-case analysis and the sensitivity analysis, respectively, are reported in Supporting Tables S5-S9.

COST OF HCV HEALTH STATES

The use of health care resources was based on the actual disease status of real-life patients entered in the model. Annual health care costs were associated with their respective disease status. The cost of the resources related to each HCV health state, used for the implementation of the model, was quantified from the perspective of the Italian National Health Service by the permanent members of the Workshop of Economics and Drugs in Hepatology, as reported.[23] Unit costs were valorized using the Italian National Health Service inpatient and outpatient reimbursement tariffs. Specifically, the model accounted for costs of HCV genotyping, fibrosis staging, and therapy monitoring, including visits, blood liver tests, and HCV RNA quantification. These costs were determined using the Medicare reimbursement schedule and published

TABLE 1. Disease Progression Rates in Patients Who Reach SVR

Stage	Value (SE)	Distribution	Alpha	Beta	Source
F0 to F1/2	0.00	Beta	14.79	127.40	No progression assumed
F1/2 to F3	0.00	Beta	0.52	16.67	No progression assumed
F3 to F4	0.00	Beta	1.74	15.63	No progression assumed
F4 to DC (HE)	0.001 (0.00045)	Beta	8.70	281.30	(15,16) according to the SVRs reported in (11)*
F4 to DC (VB)	0.001 (0.00045)	Beta	8.70	281.30	(15,16) according to the SVRs reported in (11)*
F4 to DC (AS)	0.001 (0.00045)	Beta	8.70	281.30	(15,16) according to the SVRs reported in (11)*
F4 to HCC	0.010 (0.0075)	Beta	0.98	97.02	(15,16) according to the SVRs reported in (11)*
DC (HE) to HCC	0.013 (0.01)	Beta	89.90	809.10	(15) according to the SVRs reported in (11)*
DC (HE) to LT	0.015 (0.01)	Beta	107.58	870.42	(15) according to the SVRs reported in (11)*
DC (HE) to death	0.012 (0.01)	Beta	73.62	744.38	(15) according to the SVRs reported in (11)*
DC (VB) to HCC	0.013 (0.01)	Beta	89.90	809.10	(15) according to the SVRs reported in (11)*
DC (VB) to LT	0.015 (0.01)	Beta	107.58	870.42	(15) according to the SVRs reported in (11)*
DC (VB) to death	0.012 (0.01)	Beta	73.62	744.38	(15) according to the SVRs reported in (11)*
DC (AS) to HCC	0.013 (0.01)	Beta	89.90	809.10	(15) according to the SVRs reported in (11)*
DC (AS) to LT	0.015 (0.01)	Beta	107.58	870.42	(15) according to the SVRs reported in (11)*
DC (AS) to death	0.012 (0.01)	Beta	73.62	744.38	(15) according to the SVRs reported in (11)*
HCC to LT year 1	0.20 (0.01)	Beta	319.80	1,279.20	(17)
HCC to death	0.43 (0.01)	Beta	1,053.50	1,396.50	(17)
LT, year 1 to death	0.15 (0.01)	Beta	191.10	1,082.90	(17)
LT, post to death	0.057 (0.01)	Beta	30.58	505.93	(17)

*The respective references used are reported in Supporting Tables S6 and S7.
Abbreviations: AS, ascites; DC, decompensated cirrhosis; HE, hepatic encephalopathy; LT, liver transplantation; VB, variceal bleeding.

literature. The frequency of monitoring visits and tests was based on HCV treatment guidelines and clinical judgment. The costs of outpatient specialist visits and diagnostic tests were estimated according to the national medical care payment databases (national tariffs) defined by the list of charges for specialist medical and outpatient services, as updated by the Italian Ministry of Health in October 2012. The Diagnosis Related Group system currently in use was applied as a proxy for the costs of hospitalization due to decompensated cirrhosis and HCC.[14]

The annual discount rate applied to costs was 3%. The costs and the sources of the data on costs used in the analysis are reported in the Supporting Information. The costs of IFN-free treatments currently vary by country and are negotiated with specific discount policies. The base-case analysis was carried out under the hypothetical price of €15,000 per patient, considering this to be the mean cumulative price of a 12-week IFN-free DAA regimen negotiated in Italy (Supporting Table S11).

MODEL OUTCOMES

The outcomes of the model are expressed in terms of quality-adjusted life-years (QALYs). The rationale for choosing the cost utility for the cost-effectiveness analysis was that this analysis was not designed to compare the effectiveness of two different drug combinations but instead to evaluate two scenarios of the same treatment, which strongly impacts quality of life, as well as years of life gained. The utilities used are reported in Supporting Tables S13 and S14. Health benefits were discounted by 3%. The utility value of patients in fibrosis stages F0-F3 post-SVR was

TABLE 2. Disease Progression Rates in Patients Without SVR

Stage	Value (SE)	Distribution	Alpha	Beta	Source
F0 to F1/2	0.10 (0.03)	Beta	14.79	127.40	(18)
F1/2 to F3	0.03 (0.04)	Beta	0.52	16.67	(17)
F3 to F4	0.10 (0.07)	Beta	1.74	15.63	(15)
F4 to DC (HE)	0.03 (0.01)	Beta	8.70	281.30	(15)
F4 to DC (VB)	0.03 (0.01)	Beta	8.70	281.30	(15)
F4 to DC (AS)	0.03 (0.01)	Beta	8.70	281.30	(15)
F4 to HCC	0.05 (0.01)	Beta	23.70	450.30	(15)
DC (HE) to HCC	0.10 (0.01)	Beta	89.90	809.10	(15)
DC (HE) to LT	0.11 (0.01)	Beta	107.58	870.42	(15)
DC(HE) to death	0.09 (0.01)	Beta	73.62	744.38	(15)
DC (VB) to HCC	0.10 (0.01)	Beta	89.90	809.10	(15)
DC (VB) to LT	0.11 (0.01)	Beta	107.58	870.42	(15)
DC (VB) to death	0.09 (0.01)	Beta	73.62	744.38	(15)
DC (AS) to HCC	0.10 (0.01)	Beta	89.90	809.10	(15)
DC (AS) to LT	0.11 (0.01)	Beta	107.58	870.42	(15)
DC (AS) to death	0.09 (0.01)	Beta	73.62	744.38	(15)
HCC to LT Year 1	0.20 (0.01)	Beta	319.80	1,279.20	(17)
HCC to death	0.43 (0.01)	Beta	1,053.50	1,396.50	(17)
LT, year 1 to death	0.15 (0.01)	Beta	191.10	1082.90	(17)
LT, post to death	0.057 (0.01)	Beta	30.58	505.93	(17)

Abbreviations: AS, ascites; DC, decompensated cirrhosis; HE, hepatic encephalopathy; LT, liver transplantation; VB, variceal bleeding.

assumed to be 1, presuming a state of full health after SVR. No changes in utility values were considered for the other fibrosis stages (>F3), even if after SVR in the base-case analysis. In the sensitivity analysis the utilities were varied according to a beta variable in order to take into account potential variability in national quality of life values. In the base-case analysis we assumed that the mortality rate of people affected by chronic HCV infection in stages F0-F3 coincided with the mortality rate of the general population (Supporting Table S4).

INCREMENTAL COST-EFFECTIVENESS ANALYSIS

The model produces discounted lifetime QALYs and direct medical costs for each treatment policy. The ICER was calculated as the ratio of the difference in costs over the differences in QALYs between the two policies. We tested whether policy 1 compared to policy 2 produced an ICER below the willingness to pay (WTP) threshold generally taken into account by the National Institute for Clinical Excellence, a UK agency (i.e., €20,000-40,000/QALY).[24]

MULTIVARIATE SENSITIVITY ANALYSIS

A sensitivity analysis was conducted to test the robustness of the study results. The average values and standard errors were used to derive the scale and shape of the parameters of each model input (alpha and beta, Tables 1 and 2). Gamma random variables for cost drivers and beta random variables for utilities, transitions, and SVR were assumed, which is in accordance with the methodological guidelines of the International Society of Pharmacoeconomics and Outcomes Research.[25] To account for all of the ICER realizations given the simultaneous variation of each parameter included in the model (transition probabilities, SVR, and utility), a Monte Carlo analysis with 10,000 simulations was conducted. The distribution of ICERs obtained in the simulation was presented on a cost-effectiveness plot showing the incremental costs and incremental QALYs resulting from each model realization. Furthermore, the cumulated distribution was plotted on a cost-effectiveness acceptability curve, which allows for observation of the probability of the ICER being under a certain threshold representing the WTP of a third-party payer for a QALY gained. The model was constructed using Excel Visual Basic.

RESAMPLING SCENARIO

To generalize the results of our study to different European contexts, a scenario analysis was performed. The population was reassembled to take into account different distributions of populations among fibrosis levels in different European countries. Resampling was performed by increasing (or decreasing) the original population of PITER in each level of fibrosis by using a uniform random variable ranging from 0 to 1.

In the sensitivity analysis, the transition probabilities were assumed to follow a nonlinear progression by associating an exponential variable ranging from 0 to 1 with each transition probability. Moreover, we characterized the transition probabilities using "under staging" and "over staging" variables. Thus, applying a further increase of exponential distribution, we assumed different rates for later disease stages (F3 and F4) compared to stages F0-F3. We considered also the diagnostic accuracy of methods to assess fibrosis, in that a certain proportion of patients with F3 probably have F4 liver fibrosis which has been underdiagnosed (and this is true for all methods used to assess fibrosis, both histological and noninvasive). This uncertainty was taken into account to model the utility value for fibrosis stages F0-F3 post-SVR.[26]

In this scenario analysis, the consumption of resources related to each HCV health state was quantified based on updated data that included costs by HCV health state reported in France, Germany, Italy, Romania, and the United Kingdom. Average costs of disease stages were calculated (Supporting Table S10).[23,27-30]

To take into account higher hypothetical prices associated with HCV treatment, we included in the scenario analysis the price variation ranging from €15,000 to €40,000 (the mean hypothetical European price considered for the scenario analysis was €30,000).

HCV patient mortality was adjusted using an exponential random distribution to account for its variability.

We used a tornado graph to illustrate the response of the European ICER to the variability of each parameter considered for the scenario analysis.

DECREASING DAA PRICE SCENARIO

To determine whether policy 1 became dominant (i.e., less costly and more effective than policy 2), a scenario analysis on decreasing DAA regimen prices was

also conducted. The minimum price of €15,000 was assumed to have remained stable for patients in the F3 or F4 stage of liver fibrosis, whereas the price was lower for patients with mild liver disease, applying two differentiated discount levels. Specifically, the price for patients in the F0 stage was discounted at a different rate from that for patients in the F1/F2 stage. Different price combinations were simulated, and the sensitivity analysis defined the level of prices in which policy 1 became dominant.

ETHICS

The protocol of the HCV cohort study was approved by the ethics committee of the Italian National Institute of Public Health and by each of the local ethics committees of the participating clinical centers.[12]

Results

BASE-CASE ANALYSIS

The median age of the study population was 58 years (range 20-95 years). At the DAA IFN-free price of €15,000, treating all patients regardless of fibrosis stage (policy 1) cost €301,788,399 and produced 93,131 QALYs. On the other hand, treating prioritized patients first and the remaining patients once they reached the F3 fibrosis stage cost €269,841,561 and produced 89,490 QALYs. Treating all stages of fibrosis compared with treating only "prioritized" patients increased costs by €31,946,839, whereas the incremental QALYs were 3,641. The ICER of policy 1 was €8,775/QALY gained. Policy 1 was therefore cost-effective compared to the threshold value generally taken into account by the National Institute for Clinical Excellence.[24]

MULTIVARIATE PROBABILISTIC SENSITIVITY ANALYSIS

The results of the Monte Carlo probabilistic analysis are shown in Fig. 2. Most points on the cost-effectiveness plot (Fig. 2A) are distributed in the northeast quadrant, showing that policy 1 was associated with higher costs and greater benefits than policy 2. The curve in Fig. 2B shows that when treating all stages of liver disease, ICERs remained below €30,000/QALY gained in 94% of the simulations assumed and below €40,000/QALY gained in 97%.

RESAMPLING EUROPEAN SCENARIO ANALYSIS

The ICER of the European scenario analysis (DAA mean price €30,000) was €19,541.75/QALY gained. It was therefore cost-effective compared to the threshold value generally taken into account by the National Institute for Clinical Excellence.[24] The most sensitive parameter was the HCV treatment price (Fig. 3). The ICER varied from €9,107.60/QALY when the DAA regimen price was €15,000 to €26,497.84/QALY when the DAA regimen price was €40,000. The ICER was also sensitive to variations in the utility value of patients in fibrosis stages F0-F3 post-SVR and in the transition probabilities from F0-F3, whereas no impact in ICER was observed for the transition probabilities from F3 to F4. A slight impact on ICER was observed for the population in fibrosis stage F1-F2, whereas ICER was not sensitive to variations in other variables analyzed (Fig. 3).

DECREASING DAA PRICE SCENARIO ANALYSIS

Considering variables with the highest impact on ICER obtained by the sensitivity scenario analysis (i.e., DAA price and transition probabilities), 15 different combinations of price levels differentiated by fibrosis stage and discount rate (Fig. 4; Supporting Table S15) were evaluated. The ICERs decrease with decreasing price levels of the treatment regimens in patients with F0 fibrosis, until reaching dominance, meaning lower costs and higher benefits in terms of QALY gained for policy 1 compared to policy 2. For discounts of the base price of at least 75% applied in patients with F0-F2 fibrosis, policy 1 became dominant.

The Monte Carlo analysis, for the DAA regimen price of €15,000 for patients with fibrosis stage F3 or higher and €3,750 for patients with fibrosis stage F0-F2 (75% discount) shows that in 41% of scenarios policy 1 was dominant and the ICER fell below the threshold of €30,000/QALY gained in 99.4% of scenarios and below €40,000/QALY gained in 99.5% of scenarios (Supporting Fig. S3).

Discussion

The World Health Organization foresees the elimination of HCV infection by 2030, through achieving such global targets as a 65% reduction in HCV-related deaths and the treatment of 80% of eligible persons

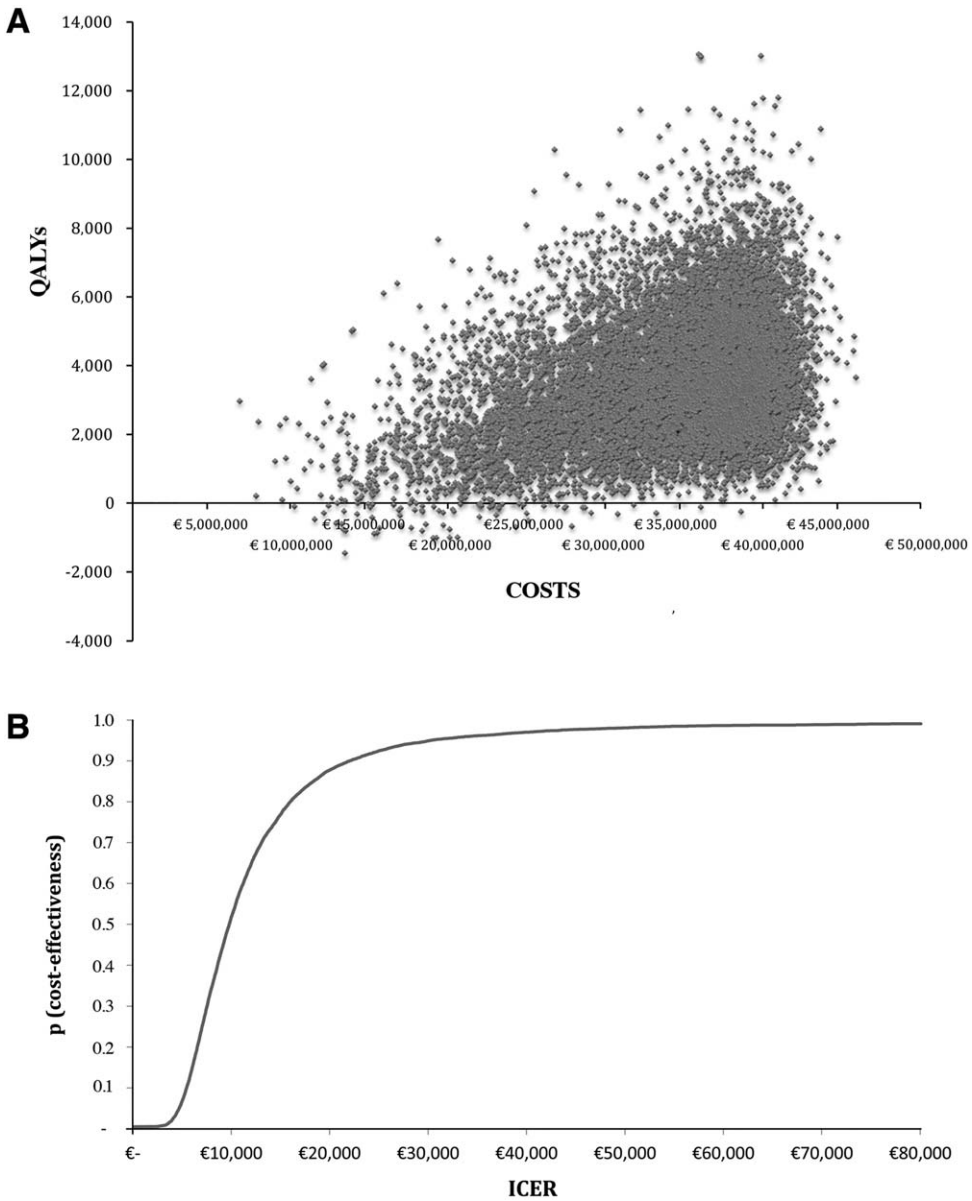

FIG. 2. (A) Cost-effectiveness plot according to Monte Carlo probabilistic sensitivity analysis. The Monte Carlo scenarios (10,000) were arranged on a cost-effectiveness plot and then reported on a cost-effectiveness acceptability curve. Probabilistic results were depicted using a cost-effectiveness plane, which consists of a four-quadrant diagram, where the *x* axis represents the additional total cost of implementing this outcome and the *y* axis represents the incremental level of effectiveness of an outcome. Most of the ICERs (calculated as incremental costs by the incremental QALYs comparing policy 1 to policy 2) reported in the cost-effectiveness plane are associated with positive incremental health consequences and costs, as in quadrant 1 of the cost-effectiveness plane. (B) Cost-effectiveness acceptability curve. The results of 10,000 Monte Carlo simulations (probabilistic sensitivity analysis) in which all input variables are varied simultaneously based on the listed ranges are reported. The graph shows the percentage of simulations in which policy 1 was considered cost-effective compared with policy 2, depending on the WTP threshold. As the WTP increases (from left to right on the *x* axis), the percentage of simulations resulting in the "universal" treatment of all patients being cost-effective also increases. For example, for treatment at a WTP of €30,000/QALY, treating all patients is cost-effective in 94% of cases; at a WTP of € 40,000/QALY, treating all patients is cost-effective in 97% of cases.

with chronic HCV infection.[31] In light of this and the current, nearly worldwide restrictions in DAA accessibility, we evaluated the costs and benefits of two scenarios of access to DAAs, populating the Markov model with a real-life cohort of patients. Because the cohort can be reasonably considered to be a

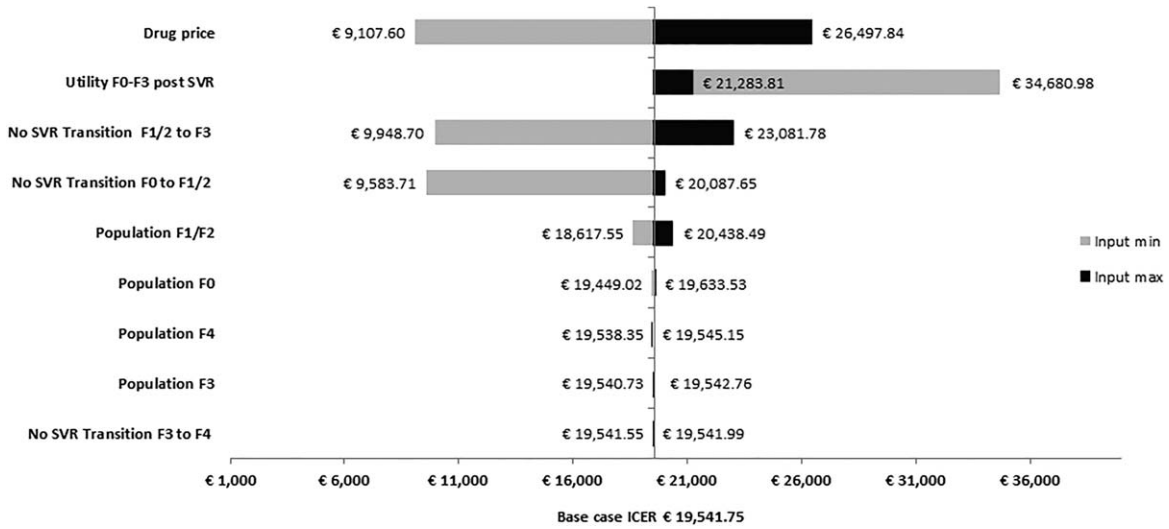

FIG. 3. Sensitivity European scenarios. The tornado diagram depicts the results of one-way sensitivity analysis for the inputs that were varied in the scenario analysis. The vertical line corresponds to all the parameters at their respective base values (mean DAA price €30,000) and represents the ICER in the base-case analysis (€19,541.75/QALY gained). The horizontal bars represent the variation of the ICER, given variations of parameters of scenario analysis. The bars to the right of the base-case ICER indicate an increase in the ICER relative to the base case to the upper limit of the input variable; the bars to the left indicate the inverse. The longest bar (reflecting the parameter generating the major impact) is placed at the top, and the other bars are arrayed in descending order of length (i.e., when the price increases from €15,000 to €40,000, the ICER increases). The black bars indicate a direct correlation between the increase in the parameter's value and the ICER, whereas the gray bars indicate an inverse correlation. The HCV treatment price is the parameter with the greatest effect on the ICER, in that it has the highest range as the absolute value of the difference between the upper and the lower inputs followed by utility value variations and transition probabilities from F0-F3.

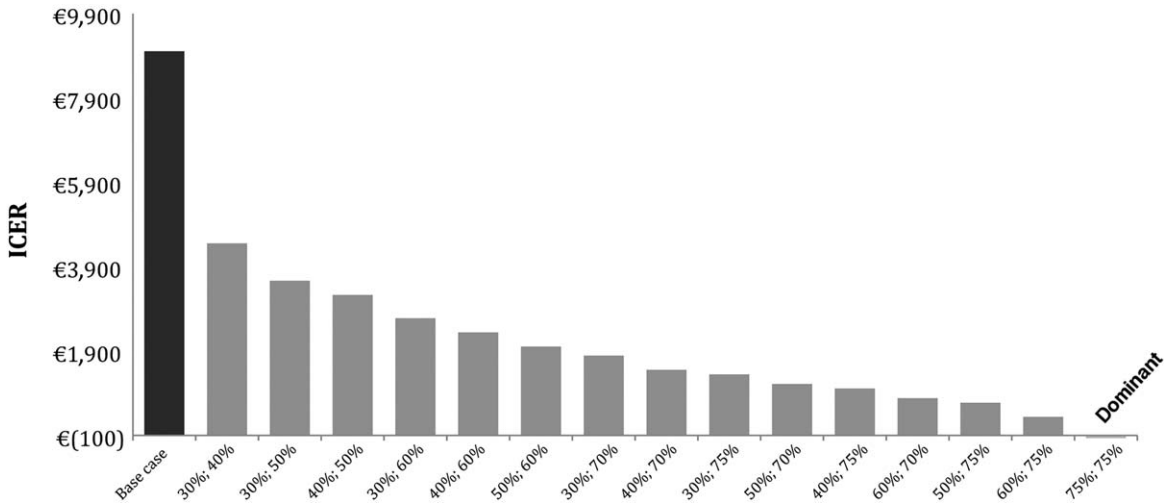

FIG. 4. Decreasing price scenarios. ICERs were determined for 15 different combinations of price levels differentiated by fibrosis stage and discount rates and are presented as vertical bars. The first column corresponds to the ICER obtained applying the base price (€15,000). The columns that follow the first report each ICER obtained using the discounted DAA regimen costs, as indicated in percent on the *x* axis for stages of fibrosis F0 (the first percent number) and F1/F2 (the second percent number). ICERs continued to decrease with decreasing price levels of the treatment regimens in patients with F0 fibrosis, until reaching dominance for discounts of the base price of at least 75%, applied in patients with F0-F2 fibrosis.

representative sample of patients in care without any kind of clinical, sociodemographic, or insurance restrictions,[12] the only assumptions reflected in the results are those made for the model and not made on a hypothetical population. The ICERs calculated for Italy and those obtained in the European DAA treatment scenario have shown an overall cost-effectiveness below the WTP threshold. The cost of treating this large population, independently of fibrosis stage, is still high, yet in the long run it is much less expensive than treating only those with advanced fibrosis, as indicated by the ICERs which ranged from €8,775 to €19,541.75/QALY gained. This model provides important insight into extending access to DAAs to patients in earlier fibrosis stages, even those of advanced age.

The cost-effectiveness of treating all HCV-infected patients, regardless of disease severity, refers to a population with a mean age of 59 years, which in part reflects that of the general population of HCV patients in Europe and populations in other parts of the world that have similar epidemiologic characteristics (i.e., individuals infected many years previously through blood transfusion or nosocomial transmission with historical trends of high incidence of infection).[32-34] Our results indicate that the wide use of DAA regimens in Europe has a good cost-effectiveness profile; however, in different countries, the effects of the therapies vary significantly, and specific population-based health policies are required.[35] The ICER that was produced using the Italian and the European scenario could be generalized to populations that are similar in terms of age and liver-disease stage. In countries where the epidemiology of HCV infection is quite different, such as in the United States (excluding baby boomers), the higher drug prices would obviously increase the ICER. However, because the HCV-infected population in the United States is younger than our population, greater benefits would result, which would contribute to decreasing the ICER.

In this study, a probabilistic sensitivity analysis was carried out by varying main model inputs (i.e., treatment efficacy, the utility of each health state, transitions, and costs).[36] Specifically, for policy 1, cost-effectiveness was confirmed in 94%-97% of the 10,000 simulations, in that the ICERs remained considerably below the accepted threshold, indicating substantial health gains in this real-life cohort. These cost-effectiveness results are supported by clinical data. Treating only patients in advanced stages of fibrosis is a negative predictor of the SVR, and it does not prevent the progression of liver disease or HCC development in all patients, although the progression rate is lower than that among untreated patients.[3,19-22,37] Although the impact of comorbidities was not evaluated, the comorbidity pattern could negatively influence the long-term effectiveness and the mortality rate not related to HCV following the "delayed" versus the "universal" treatment. On the other hand, HCV-related disease inflicts a huge economic and clinical burden, also as a result of the infection's extrahepatic comorbidities, and early HCV eradication will reduce these burdens.[38-40] Furthermore, although delaying treatment is an attractive option for insurers, it fails to take into account the clinical and economic benefits of early treatment in terms of prevention and quality of life.[40,41] These additional clinical and prevention rationales, coupled with the results of this study, further support the notion that the reported cost-effectiveness data could translate into additional clinical and economic benefits and strongly indicate the necessity to move from the urgency to treat select patients to access for all chronically infected patients.

The health of a human being is always cost-effective. However, the sustainability of innovations is a challenge for health systems, and a variety of strategies need to be tested. Despite the very good cost-effectiveness profile obtained in this study, affordability is one of the main factors that determine the prescribing of DAAs for all patients. Budget impact analyses are required for each country in order to determine how to afford the high initial investment, which in the long run is cost-effective.

In the scenario analysis, we went beyond a cost-effectiveness analysis, varying the price of treatment regimens for different stages of fibrosis. If the price remains unvaried for patients with the severest disease (i.e., those who are currently treated) yet is lowered for less severe patients (patients who do not yet have access to treatment), then treating HCV infection has a much more favorable cost-effectiveness profile and could become cost-saving.

This study has several limits that could affect the robustness of the model and the impact of the results. Specifically, we considered only patients who were aware of their HCV infection. In the base-case analysis, we used single transition rates for all ages and genders. Fibrosis stage is classified according to noninvasive measurement which, although widely used, has limits in diagnostic accuracy, specifically with regard to the definition of fibrosis stages F3-F4. Using the nonlinear progression of liver disease and a further

exponential distribution in F3-F4 stages of liver fibrosis, we could have at least partly avoided the possible bias of "understaging" or "overstaging" of liver disease. In addition, patients from F3-F4 to cirrhosis have prioritized treatment, and modeling this assumption could have better approximated the reality of prioritized patients.

The model does not distinguish patients on the basis of alcohol consumption, metabolic syndrome, or comorbidities, although these factors may affect treatment outcomes and costs. These factors are more common in patients with fibrosis stage higher than F3, and their impact on the results might be minimal, given that this group of patients was included in both treatment scenarios. The costs of managing adverse effects were not estimated; however, DAAs do not have adverse effects that could significantly impact the model. Patients with severe liver disease could have had more adverse effects following DAA treatment, yet this group of patients was equally represented in both scenarios. The regression of liver fibrosis after successful treatment was not taken into consideration, whereas patients who do not reach SVR proceed through the natural history of liver disease progression without being retreated. These assumptions may have led to the ICERs having been overestimated. The reinfection rate was not considered, which could have produced an underestimate in the ICER. Discontinuation of therapy and retreatment were not considered, which could have resulted in the costs having been underestimated. On the other hand, the societal impact of antiviral treatment has not been considered, and the exclusion of societal costs from the analysis may have led to our having underestimated the value of the universal versus prioritized treatment. One potential limit of this study concerns the differences in the distribution of the population among fibrosis stages and therefore the potential QALY gain, which is associated with the individuals' health states. To limit the effect of this possible bias in the ICER estimation, in the multivariate sensitivity analysis, utilities as well as transition probabilities were varied for the base-case and for the European scenario analysis. Moreover, in the latter analysis the original population was resampled to better represent a population of infected HCV patients in care who would not be necessarily Italian.

In conclusion, at a base price of €15,000 for a DAA regimen in Italy and at a mean European price of €30,000, treating HCV infection at early stages of fibrosis appeared to improve health outcomes and to be cost-effective. Cost-effectiveness increased significantly, becoming cost-saving when varying the price of treatment regimens in early stages of fibrosis. Specifically, for the price levels that were lower than 75% of the base price (€15,000) applied in patients with F0-F2 fibrosis stage, policy 1 (i.e., "universal treatment") became dominant (lower costs and greater benefits in terms of QALYs) compared to policy 2 (i.e., "prioritized treatment").

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REFERENCES

1) Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558-567.
2) World Health Organization. Hepatitis C. Fact sheet. http://www.who.int/mediacentre/factsheets/fs164/en/. Published April 2017. Accessed May 30, 2017.
3) Razavi H, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. HEPATOLOGY 2013;57:2164-2170.
4) Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet 2016;388:1081-1088.
5) Chung RT, Baumert TF. Curing chronic hepatitis C—the arc of a medical triumph. N Engl J Med 2014;370:1576-1578.
6) Lange CM, Jacobson IM, Rice CM, Zeuzem S. Emerging therapies for the treatment of hepatitis C. EMBO Mol Med 2014;6:4-15.
7) Thomas DL. Global control of hepatitis C: where challenge meets opportunity. Nat Med 2013;19:850-858.
8) Reau NS, Jensen DM. Sticker shock and the price of new therapies for hepatitis C: is it worth it? HEPATOLOGY 2014;59:1246-1249.
9) Obach D, Yazdanpanah Y, Esmat G, Avihingsanon A, Dewedar S, Durier N, et al. How to optimize HCV treatment impact on life years saved in resource-constrained countries. HEPATOLOGY 2015;62:31-39.
10) European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. J Hepatol 2017;66:153-194.
11) American Association for the Study of Liver Diseases. HCV guidance: recommendations for testing, managing, and treating hepatitis C. http://hcvguidelines.org. Accessed November 3, 2016.
12) Kondili LA, Vella S; PITER Collaborating Group. PITER: an ongoing nationwide study on the real-life impact of direct acting antiviral based treatment for chronic hepatitis C in Italy. Dig Liver Dis 2015;47:741-743.
13) Alagoz O, Hsu H, Schaefer AJ, Roberts MS. Markov decision processes: a tool for sequential decision making under uncertainty. Med Decis Making 2010;30:474-483.

14) Romano F, Ruggeri M, Coretti S, Giannini EG, Sacchini D, Annichiarico BE, et al. Economic assessment of eltrombopag in the treatment of thrombocytopenia. Expert Rev Pharmacoecon Outcomes Res 2015;15:713-720.
15) Dienstag JL, Ghany MG, Morgan TR, Di Bisceglie AM, Bonkovsky HL, Kim HY, et al.; HALT-C Trial Group. A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C. HEPATOLOGY 2011;54:396-405.
16) Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al.; HALT-C Trial Group. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. HEPATOLOGY 2010;52:833-844.
17) Wright M, Grieve R, Roberts J; UK Mild Hepatitis C Trial Investigators. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess 2006;10:1-113.
18) Townsend R, McEwan P, Kim R, Yuan Y. Structural frameworks and key model parameters in cost-effectiveness analyses for current and future treatments of chronic hepatitis C. Value Health 2011;14:1068-1077.
19) Di Marco V, Calvaruso V, Ferraro D, Bavetta MG, Cabibbo G, Conte E, et al. Effects of eradicating hepatitis C virus infection in patients with cirrhosis differ with stage of portal hypertension. Gastroenterology 2016;151:130-139.
20) Petta S, Di Marco V, Bruno S, Enea M, Calvaruso V, Boccaccio V, et al. Impact of virus eradication in patients with compensated hepatitis C virus–related cirrhosis: competing risks and multistate model. Liver Int 2016;36:1765-1773.
21) Lawitz EJ, Ruane P, Stedman C, Foster GR, Hyland RH, Coogan S, et al. Long-term follow-up of patients with chronic HCV infection following treatment with direct acting antiviral regimens maintenance of SVR, persistence of resistance mutations and clinical outcomes. J Hepatol 2016;64:S612-S613.
22) Bruno S, Zuin M, Crosignani A, Rossi S, Zadra F, Roffi L, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long term prospective study. Am J Gastroenterol 2009;104:1147-1158.
23) Ruggeri M, Coretti S, Gasbarrini A, Cicchetti A. Economic assessment of an anti-HCV screening program in Italy. Value Health 2013;16:965-972.
24) Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). Lancet 2002;360:711-715.
25) Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD; ISPOR-SMDM Modeling Good Research Practices Task Force. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. Value Health 2012;15:835-842.
26) Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, et al.; FIBROSTIC Study Group. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). J Hepatol 2010;53:1013-1021.
27) Schwarzinger M, Deuffic-Burban S, Mallet V, Pol S, Pageaux GP, Canva-Delcambre V, et al. Lifetime costs attributable to chronic hepatitis C from the French healthcare perspective. J Hepatol 2013;58:S21-S22.
28) Stahmeyer JT, Schauer S, Rossol S, Wedemeyer HH, Wirth D, Bianic F, et al. Cost-effectiveness of triple therapy with telaprevir for chronic hepatitis C virus patients in Germany. JHEOR. 2013;1:239-253.
29) McEwan P, Ward T, Webster S, Kalsekar A, Brenner M, Yuan Y. Estimating the cost-effectiveness of 12 weeks of daclatasvir+sofosbuvir in patients chronically infected with HCV genotype 3. J Hepatol 2015;62:S666-S667.
30) Ortsäter G. Burden of hepatitis C in Europe—the case of France and Romania. Presented to: European Liver Patients Association, 2015. http://www.vhpb.org/files/html/Meetings_and_publications/Presentations/LOND33.pdf.
31) World Health Organization. Draft global health sector strategy on viral hepatitis 2016-2021—the first of its kind. http://www.who.int/hepatitis/strategy2016-2021/Draft_global_health_sector_strategy_viral_hepatitis_13nov.pdf. Published November 2015. Accessed November 3, 2016.
32) Guadagnino V, Stroffolini T, Rapicetta M, Costantino A, Kondili LA, Menniti-Ippolito F, et al. Prevalence, #risk |factors, and genotype distribution of hepatitis C virus infection in the general population: a community-based survey in southern Italy. HEPATOLOGY 1997;26:1006-1011.
33) Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. HEPATOLOGY 2013;57:1333-1342.
34) Smith BD, Beckett GA, Yartel A, Holtzman D, Patel N, Ward JW. Previous exposure to HCV among persons born during 1945-1965: prevalence and predictors, #United |States, 1999-2008. Am J Public Health 2014;104:474-481.
35) Deuffic-Burban S, Deltenre P, Buti M, Stroffolini T, Parkes J, Mühlberger N, et al. Predicted effects of treatment for HCV infection vary among European countries. Gastroenterology 2012;143:974-985.
36) Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. Health Econ 1994;3:95-104.
37) **Foster GR**, **Irving WL**, Cheung MC, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224-1231.
38) Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology 2015;149:1345-1360.
39) Petta S, Maida M, Macaluso FS, Barbara M, Licata A, Craxì A, et al. Hepatitis C virus infection is associated with increased cardiovascular mortality: a meta-analysis of observational studies. Gastroenterology 2016;150:145-155.
40) Younossi Z, Park H, Henry L, Adeyemi A, Stepanova M. Extrahepatic manifestations of hepatitis C: a meta-analysis of prevalence, quality of life, and economic burden. Gastroenterology 2016;150:1599-608.
41) Martin NK, Vickerman P, Dore GJ, Grebely J, Miners A, Cairns J. Prioritization of HCV treatment in the direct-acting antiviral era: an economic evaluation. J Hepatol 2016;65:17-25.

Author names in bold designate shared co-first authorship.

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