Cost–effectiveness analysis of simeprevir with daclatasvir for non-cirrhotic genotype-1b-naïve patients plus chronic hepatitis C

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Background: The cost of interferon-free combination therapies remains high to provide widespread access to treatment, regardless of fibrosis stage. Aim: To estimate the cost–effectiveness of simeprevir/daclatasvir (SMV/DCV) therapy in treatment-naïve chronic hepatitis C genotype-1b patients with moderate fibrosis. Methods: A Markov model was developed to simulate the natural history of chronic hepatitis C progression. The model estimated lifetime healthcare costs and quality-adjusted life-years (QALY) for a cohort of patients from the Spanish National Healthcare System perspective. The cost–effectiveness threshold considered was €40,000/QALY. The treatment strategies analyzed were SMV/DCV, peginterferon/ribavirin/telaprevir, and peginterferon/ribavirin/boceprevir. A sensitivity analysis was carried out. Results: The incremental cost–effectiveness ratios of the SMV/DCV strategy were €23,774/QALY and €28,524/QALY compared with that of telaprevir or boceprevir triple therapy, respectively, for genotype-1b patients with moderate fibrosis. Conclusions: SMV/DCV combination compared with the standard of care previous to the arrival of second-generation direct-acting antivirals fell below generally accepted willingness-to-pay threshold. Results obtained should be supported by ongoing clinical trials.

KEYWORDS: boceprevir • chronic hepatitis C • cost–effectiveness • daclatasvir • direct acting antivirals • pegylated interferon • protease inhibitors • ribavirin • simeprevir • telaprevir

Hepatitis C virus infection (HCV) is the main cause of chronic hepatic disease and the leading indication for liver transplantation [1].

The most prevalent region in Europe for chronic infection with the HCV is the south, but there are important fluctuations among countries with respect to genotype distribution. The most common genotype in Europe is genotype-1b, unlike in the USA, where genotype-1a is more common [2]. In Spain, 69% of patients with chronic infection with the HCV are infected by genotype 1, =63% of which is subtype 1b [3].

The aim of pharmacologic treatment is to achieve the sustained viral response (SVR), defined as the absence of viremia 12 weeks after treatment has ended. Most relapses occur in the first month after the end of treatment. Hence, the result after 12 weeks is in accordance with the result obtained 24 weeks after treatment, which has been the cutoff used in studies carried out in the past [4].

Treatment with peginterferon (pIFN) and ribavirin (RBV) was the standard of care (SoC) for more than a decade until the licensing of boceprevir (BOC) and telaprevir (TEL). The addition of BOC or TEL to treatment resulted in considerable enhancement of SVR rates but the safety profile worsened, along with an increase in disease progression [5,6].

Sofosbuvir (SOF), simeprevir (SMV), and daclatasvir (DCV) are a new generation of direct-acting antivirals (DAAs). The main features are a SVR over 90% in some populations, the possibility of use of an interferon-free regimen, and a potential treatment length reduction...
to 12 weeks. Treatment must be tailored to the patient (including virologic features). Accessibility to treatment according to the healthcare environment is extremely important.

The cost of such interferon-free combination therapies is €60,000–180,000 depending on the regimen and treatment duration [7]. However, the financed cost can be considerably lower in some public health systems.

Economic restrictions are a relevant factor in treatment selection. Treatment selection may have a particularly important bearing on healthcare resources consumption during antiviral therapy [8]. The budgetary impact is the main barrier to access to these new therapeutic options, so treatment for patients with low-grade fibrosis has been delayed in some healthcare systems. The high cost of treatment combinations means that treatment is not available to a large proportion of patients who could benefit from it [9–11]. It seems rational to give priority to patients with greater disease progression [12]. However, extending the treatment to patients with mild fibrosis (grade 1–2), in which it shows greater effectiveness [13], is also reasonable.

Instead of subordination of treatment onset according to the progression of fibrosis, strategies that may have a lower budgetary impact in selected subpopulation could be investigated. Treatment with SMV/DCV has been used in patients with genotype-1b at a lower cost than for other oral combinations. Studies have shown promising results, with a SVR =90% (although the quality of evidence is limited). Clinical trials using SMV/DCV are in progress and, if its effectiveness can be confirmed, such treatment could be labeled in SmPC.

In recent years, the speed with which new therapeutic options have been developed for individuals with chronic infection with the HCV has created a need for cost–effectiveness studies.

The aim of this study is to ascertain the cost–effectiveness of SMV/DCV therapy in treatment-naïve chronic hepatitis C (CHC) genotype-1b patients with moderate fibrosis based on the results of clinical trials.

Methods

Study design & analytical methods
A Markov model was created to estimate the cost and health outcomes from initiation of treatment with a lifelong time horizon (Figure 1). The duration of the cycle was 3 months. This length provides a better adjust to the disease progression than 1 year duration. A half-cycle correction was made based on recommendations [14]. The model was developed using Pro 2014 Software (TreeAge, Williamstown, MA).

The study was undertaken from the perspective of the Spanish National Healthcare System. A threshold limit of €40,000/quality-adjusted life-year (QALY) was established for cost–effectiveness [15] – this is the generally accepted value. The annual discount rate assumed for the costs and benefits was 3%, as recommended in the literature [16]. All costs were actualized to February 2015.

A combination of SMV/DCV in treatment-naïve CHC genotype-1 patients with moderate fibrosis was compared with two therapeutic alternatives: BOC/PEG/RBV and TEL/PEG/RBV. The incremental cost–effectiveness ratio (ICER) was calculated.

A cohort with 'moderate' fibrosis was selected because they could be candidates once patients with more severe CHC had been already treated.
**Treatment strategies**

The initial cohort of patients was defined according to the baseline characteristics of patients in clinical trial: 54 years of age with moderate fibrosis (grade 2–3) [17]. A cohort of treatment-naive genotype-1b CHC patients in the LEAGUE-1 study was selected to evaluate the efficacy of SMV/DCV [17].

SVR figures for 12 weeks after completion of treatment (SVR12) was 89% in naive patients treated for 12 weeks irrespective of RBV administration. A control group was not included, similar to that for other clinical trials using DAAs. The SMV/DCV combination was well tolerated. An increased level of bilirubin was the most common adverse reaction (particularly when used with RBV) but was not clinically significant.

RBV/pIFN combinations with BOC or TEL were selected as control groups. These therapeutic options were considered to be the standard of care when treating genotype-1b patients before second-generation DDAs were provided (Table 1).

**Costs**

The costs estimations were analyzed taking into account the regimen consisting of SMV 150 mg and DCV 30 mg once daily for 12 weeks. The drugs costs, the adverse reactions costs, and the medical monitoring costs were included in the model. The drugs costs were obtained from the Health Ministry.

### Table 1. Therapeutic options.

| Therapeutic option | SVR | PSA distribution | Disutility | Drug cost (€ 2015) | Monitoring cost (€ 2015) | Total cost (€ 2015) | Source |
|--------------------|-----|------------------|------------|-------------------|----------------------|---------------------|--------|
| SIM/DCV × 12 w     | 40/45 (89) 0.76–0.95 (40, 5) | 0.0 | €5,747 | €810 | €58,287 | [17] |
| pIFN/RBV/BOC†      | 140/209 (67) 0.60–0.73 (140, 69) | –0.019 | €26,034 | €2308 | €28,342 | [6,19] |
| SIM/DCV × 12 w     | 40/45 (89) 0.76–0.95 (40, 5) | 0.0 | €5,747 | €810 | €58,287 | [17] |
| pIFN + RBV + TEL†  | 99/145 (68) 0.60–0.75 (99, 46) | –0.008 | €33,601 | €1208 | €34,809 | [5,19] |

†Ile28B-guided therapy: pIFN + RBV for Ile28B-CC patients and pIFN + RBV + protease inhibitor for Ile28B-CT y TT.

BOC: Boceprevir; CI: Confidence interval; DCV: Daclatasvir; pIFN: Peginterferon; PSA: Probabilistic sensitivity analysis; RBV: Ribavirin; SIM: Simeprevir; SVR: Sustained virological response; TEL: Telaprevir.

### Table 2. Markov model transition probabilities.

| Study (year) | From | To | Baseline annual % (range) | PSA distribution (P1, P2)† | Ref. |
|--------------|------|----|---------------------------|---------------------------|------|
| Townsend et al. (2011) | Mild hepatitis | Moderate hepatitis | 3.70 | B (12, 1267) | [23] |
| Townsend et al. (2011) | Moderate hepatitis | Comp. cirr | 5.10 | B (23, 1746) | [23] |
| Townsend et al. (2011) | Comp. cirr | Death | -- | -- | INE |
| Townsend et al. (2011) | Comp. cirr | Death | -- | -- | INE |
| Townsend et al. (2011) | Death | Mortality by age | -- | -- | INE |
| Townsend et al. (2011) | Death | Mortality by age | -- | -- | INE |
| Cardoso et al. (2010) | Decomp. cirr | HCC | 0.50 | -- | [24,25] |
| Cardoso et al. (2010) | Transpl. 1st year | Death | 1.40 | B (14, 1365) | [26] |
| Cardoso et al. (2010) | Transpl. Next. | Death | 4.00 | B (76, 504) | [26] |
| Fattovich et al. (1997) | Comp. cirr | HCC | 1.00 | -- | [24,25] |
| Fattovich et al. (1997) | Comp. cirr | Death | 1.40 | B (14, 1365) | [26] |
| Fattovich et al. (1997) | HCC | Death | 1.40 | B (76, 504) | [26] |
| Fattovich et al. (1997) | HCC | Transplant | 42.70 | -- | [26] |
| Fattovich et al. (1997) | Transplant | Death | 2.00 | -- | [26] |
| Fattovich et al. (1997) | Death | Death | 3.00 | -- | [26] |

†PSA parameters are adjusted to quarterly values, as used in the model.

Comp. cirr: Compensated cirrhosis; Decomp cirr: Decompensated cirrhosis; HCC: Hepatocarcinoma; INE: Instituto Nacional de Estadistica; P1: Parameter 1; P2: Parameter 2; PSA: Probabilistic sensitivity analysis; SVR: Sustained virological response; Transpl: Transplant.
database except for RBV and pIFN because there are therapeutic alternatives available subjected to considerable discounts [18]. Costs were calculated based on the regimens in the clinical trials and summary of product characteristics, and assuming perfect adherence to treatment (Table 1). Acquisition costs were identical for preparations of 30 and 60 mg DCV. With regard to the control group, estimations have been previously described in depth [7,19]. Costs of RBV and pIFN were estimated from a daily dose of 1000 mg RBV and a weekly dose of 180 mg pIFN alfa-2a (ADVANCE study) or 100 μg pIFN alfa-2b (SPRINT-2 study) [5,6].

Adverse reactions led to increments in treatment costs because of, for example, medical tests/visits, drug prescriptions, and hospital admissions. Only the side effects with impact on total cost were considered that was associated with the control group (BOC and TEL regimes) and not the SMV/DCV regimen.

Monitoring costs were estimated based on the healthcare resources spent during treatment and according to detailed calculations described previously [19–22]. Costs of disease progression were obtained from the accounting system of the Basque Health Service by discriminating between ‘transition costs’ and ‘state costs’.

Markov model & transition probabilities
Transition probabilities have been used widely in published models. They were obtained from the literature and by revision by Townsend et al. (Table 2) [7,19–30].

For patients who achieved a SVR from mild/moderate CHC, the prevalence of disease progression was compared with that for the general population without CHC. By contrast, it was considered that CHC could progress despite achievement of a SVR in cirrhotic patients. However, the probability of transition would be lower if a SVR could be achieved [24,25]. The patients were classified according to the first hepatic decompensation: ascites; hepatic encephalopathy; gastrointestinal hemorrhage due to portal hypertension; and severe bacterial infection [31]. Based on this classification, the probabilities of death, hepatocellular carcinoma and liver transplantation were calculated. The potential patients for liver transplantation could have decompensated cirrhosis or hepatocellular carcinoma. Indeed, a large proportion of liver transplants are due to hepatocellular carcinoma [29].

Quality of life
Costs, life years gained, and QALYs were estimated for each therapeutic option from data on mortality, morbidity, and quality of life. A lack of direct data from the Spanish population led us to consider ‘utilities’ obtained from a sample of UK patients using the EuroQol Quality of Life Scale (EQ-5D) and Time Trade-Off method [19,32–34]. Different utility values were applied to patients who achieved a

| Health state | HRQL (QALYs) | Therapy disutility (QALYs) |
|--------------|--------------|----------------------------|
|              | Baseline (range) | PSA (P1,P2) |
| Mildhep      | 0.77          | β (480, 143.38) |
| SVR mild     | 0.82          | β (52, 12.7)   |
| Moderate hep | 0.66          | β (165, 90.15) |
| SVR mod      | 0.77          | β (130, 38.8)  |
| Cirrosis     | 0.55          | β (50, 40.91)  |
| SVR cirrosis | 0.61          | β (110, 64)    |
| Decomp. cirr| 0.45          | β (110, 134.44)|
| HCC          | 0.45          | β (110, 134.44)|
| Transpl. 1 styr | 0.45    | β (110, 134.44)|
| Transpl. next | 0.45        | β (110, 134.44)|

| Table 4. Incremental cost–effectiveness ratios for different treatment strategies. |
|-----------------------------------------------|
| Therapeutic option | Total QALYs | Total costs (£2015) | ICER (£/QALY) | PSA % threshold < £40,000/QALY |
|--------------------|-------------|---------------------|---------------|-------------------------------|
| SIM/DCV            | 14.15       | 61,709              | 23,774        | 80%                           |
| TEL/pIFN/RBV       | 13.28       | 41,021              | 28,524        | 86%                           |
| BOC/pIFN/RBV       | 13.21       | 34,896              | 41,021        | 80%                           |

BOC: Boceprevir; DCV: Daclatasvir; ICER: Incremental cost–effectiveness ratio; pIFN: Peginterferon; PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life-years; SIM: Simeprevir; TEL: Telaprevir.
SVR according to the health state from which they were obtained (Table 3) [33,34].

Therapy disutility can be defined as the degree to which quality of life fails due to the treatment. Disutility derived from treatment side effects was considered. In the absence of comparative data among the treatment options, the disutility associated with pIFN/RBV published by Grieve et al. used in previous studies [7,19,32] was employed.

**Sensitivity analyses**

Determine sensitivity analyses were carried out to assess the influence of selected variables in the base case and their impact on the cost-effectiveness analysis (CEA).

We examined the effects of initiating treatment at different ages (30–70 years) and a lower grade of fibrosis in the original cohort. ICER estimation was performed for a relative SVR modification of ±5% for the SMV/DCV regimen; so both scenarios are justified. In the former case, an increase of DCV dose to 60 mg could be associated with SVR enhancement [35,36]. In the latter case, the efficacy reduction would be supported by the utilization of these drugs in the real-world setting.

Different settings were developed by varying the probability of transition from ‘moderate hepatitis’ to ‘cirrhosis’. Maximum and minimum values reported by Townsend et al. [23] were selected. The acquisition costs of SMV and DCV were modified considering a reduction of 20 and 40%, respectively. This scenario is feasible in view of the reduction of the ‘financed’ price in comparison with the ‘notified’ price (official) for most drugs used for CHC treatment [37]. According to published guidelines, the discount rate was 0–5% [16].

Probabilistic analyses were undertaken using a Monte Carlo simulation using 1000 iterations on the basis of guidelines set by the International Society For Pharmacoeconomics and Outcomes Research [38]. The cost-effectiveness plan and acceptability curve were plotted with the results obtained. Results were arranged in accordance with the Consolidated Health Economic Evaluation Reporting Standards Statement [39].

Additional information is detailed in the **Technical Annex** [supplementary material can be found online at www.informa-healthcare.com/suppl/14737167.2015.1081061].

**Results**

**Base-case analyses**

Comparative results between SMV/DCV and other treatment options in treatment-naïve genotype-1b patients are shown in Table 4. They ranged between €23,774/QALY and €28,524/QALY depending on the selected comparator. Obtained data were below the €40,000/QALY threshold.

**Sensitivity analyses**

‘Deterministic sensitivity analyses’ show the influence of one variable modification on ICER, showing those results in Table 5. For CHC, treatment outcomes are obtained over the long term. Hence, an increase in age at treatment initiation increases the cost of QALY. In this study, the cost-effectiveness

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**Table 5. Sensitivity analyses.**

| ICER of therapeutic option versus SoC (£/QALY) | Relative effectiveness | Age at the start treatment | Discount rate | SIM/DCV cost (%) | SIM/DCV age at the start treatment |
|-----------------------------------------------|------------------------|-----------------------------|--------------|-----------------|-----------------------------------|
| SIM/DCV versus TEL/pIFN/RBV                    | <5%                    | 30                          | 0%           | 20%             | 31,204                            |
| SIM/DCV versus TEL/pIFN/RBV                    | >5%                    | 40                          | 0%           | 40%             | 18,992                            |
| SIM/DCV versus TEL/pIFN/RBV                    | 5%                     | 60                          | 5%           | 60%             | 12,635                            |
| SIM/DCV versus BOC/pIFN/RBV                   | 35,274                 | 70                          | 10%          | 50%             | 30,210                            |
| SIM/DCV versus BOC/pIFN/RBV                   | 23,244                 | 90                          | 15%          | 70%             | 49,785                            |
| SIM/DCV versus BOC/pIFN/RBV                   | 36,456                 | 110                         | 20%          | 90%             | 28,842                            |
| SIM/DCV versus BOC/pIFN/RBV                   | 23,346                 | 130                         | 20%          | 110%            | 10,564                            |
| SIM/DCV versus BOC/pIFN/RBV                   | 39,709                 | 150                         | 20%          | 130%            | 11,992                            |
| SIM/DCV versus BOC/pIFN/RBV                   | 39,709                 | 170                         | 20%          | 150%            | 11,992                            |
| SIM/DCV versus BOC/pIFN/RBV                   | 39,709                 | 190                         | 20%          | 170%            | 11,992                            |
| SIM/DCV versus BOC/pIFN/RBV                   | 39,709                 | 210                        | 20%          | 190%            | 11,992                            |
| SIM/DCV versus BOC/pIFN/RBV                   | 39,709                 | 230                        | 20%          | 210%            | 11,992                            |
threshold was exceeded only when the age was >70 years. The probability of transition to cirrhosis did not affect the result significantly.

Reduction in acquisition costs for SMV/DCV would have a relevant impact on the outcomes of analyses. In particular, the TEL/pIFN/RBV combination would be dominated by SMV/DCV if the acquisition costs decreased by 40%.

Modification in the discount rate influenced the base case. This finding is consistent with the evolution of CHC whereby the costs are incurred at the beginning and the benefits are generated in the medium-to-long term.

Probabilistic sensitivity analyses showed that 80% of simulations were below the cost–effectiveness threshold when the SMV/DCV regimen was compared with TEL/pIFN/RBV. These results were similar to those obtained on comparison of SMV/DCV with BOC/pIFN/RBV, in which 86% of simulations were below the cost–effectiveness threshold (Figures 2 & 3).

**Discussion**

One of the greatest challenges of CHC treatment is to find short-course regimens with high efficacy and good tolerance [40]. This study suggests that treatment of genotype-1b patients with moderate fibrosis with SMV/DCV could be considered efficient. The ICER compared with TEL/pIFN/RBV was €23,774/QALY and that with BOC/pIFN/RBV was €28,524/QALY. Both figures were below the threshold in our context. The univariate analysis positioned the ICER below the threshold even though the SVR for SMV/DCV decreased by 5% compared with the figures obtained in the clinical trials or the treatment initiation extended to subjects aged ≥60 years.

Achieving a value below the cost-effectiveness threshold is not the only relevant factor to implement a healthcare intervention: disease prevalence and analyses of budgetary impact are also very important. Genotype-1b is the most prevalent genotype in the Spanish population. Treatment was limited to patients who were treatment-naïve, had moderate fibrosis, and without previous resistance. Nevertheless, the target population would be considerable. If this therapeutic option is included in SmPC and acquisition costs remain lower than those for other treatments, it is highly probable that the budget impact decreases. This strategy could be reinforced if the data from the COMMIT trial are better than the results reported by the LEAGUE trial, which would probably be due to several factors (e.g., a less heterogeneous population, DCV dose of 60 mg).

With respect to the ‘off-label’ use, the SMV/DCV combination has had its role for patients with highly reduced renal function because neither drug is affected by renal clearance [41,42]. This combination could be an alternative in patients with impairment of renal function if SOF is contraindicated [43]. Moreover, interactions between SMV and DCV are not clinically relevant with immunosuppressive treatments [44]. SMV/DCV could be useful in patients undergoing renal transplantation, which is being studied in a Phase II trial [45].

One important aspect related directly to lack of adherence and therapeutic failure is the toxicity associated with treatment [46]. The safety profile of SMV/DCV with or without RBV does not seem to be comparable with strategies that include BOC and TEL. Disutility associated with protease inhibitor regimes did not influence ICER results derived from
the short length of treatment compared with the patient’s lifelong time horizon. However, poor tolerance to first-generation DAAs has been confirmed. Indeed, this study includes a reduction in quality of life during the treatment period, as well as increments in the treatment and monitoring costs of adverse reactions for the options based on BOC and TEL.

The main limitation of our study was that our results were supported by SVR percentages from a clinical trial with high clinical heterogeneity and a small number of patients in the treatment groups. Also, the DCV dose in the clinical trial was 30 mg due to a potential interaction with SMV. However, clinical relevance of this interaction was not perceived.

Therefore, CEA results would be subject to confirmation of the SVR rates in COMMIT CT (which is in progress) [35]. This trial reduces clinical heterogeneity because it limits enrollment to treatment-naïve genotype-1b patients with advanced fibrosis and without previous resistance to SMV/DCV. The relevance of determination of resistance is based on the association of two drugs with low genetic barrier, such as SMV and DCV. Also, the COMMIT study uses a DCV dose of 60 mg, which is the commonly used dose in clinical practice.

Other study limitations are the use of ‘health-related quality of life’ data obtained from UK population or the lack of efficacy data of this therapeutic strategy for the HIV coinfected patients.

Arrival of new DAAs such as SMV and SOF heralded the disappearance of BOC and TEL justified by the problems associated with drug safety. Even though they represent a new approach to CHC therapy, their stay on the therapeutic armamentarium has been extremely short. Arrival of SOF/ledipasvir or ombitasvir/paritaprevir/ritonavir with dasabuvir can generate the same situation to SMV or DCV. In this case, neither safety problems nor efficacy figures could be argued because they are well tolerated and have become part of short-term regimens without pIFN.

Access to safe and efficacious drugs can encourage competition and could reduce the acquisition costs of available DAAs and new drugs. This scenario is important in any setting, but more so in the context of budgetary constraints. Costs of combinations of SOF/SMV or SOF/DCV were ~20% higher than that for the SMV/DCV combination using official prices (notified prices). In the short term, the costs of drugs are highly volatile because the financing prices are reduced by the healthcare system as a result of market competition associated with new treatments.

The implementation of a CEA in research for new drugs is a rational demand [47]. They provide the perspective of efficiency on authorization as well as information for therapeutic positioning and prioritization. In the case of CHC, budgetary constraints remain a barrier to treatment and force prioritization among patients who are candidates for treatment. The implementation of a CEA for SMV/DCV is appropriate despite the associated uncertainty and its non-inclusion in the SmPC [48].

When the SVR was 50–70%, it was convenient to transform a subrogate variable of SVR in an outcome that allowed us to evaluate the ‘real’ impact of treatment. The parameters most widely used were the QALY and life years gained. Mathematical models can transform the intermediate measures into final results, and they contribute relevant information about the potential health outcomes of treatments. Results of use of
second-generation DAAs without pIFN achieved a SVR >90% (in some subgroups it was ≥100%). With these figures, the need for models to transform surrogate variables into QALYs may be sidelined. Cost-minimization analyses could provide relevant data to aid decision making [16] as long as there are no differences regarding tolerance, interactions, length of treatment or posology.

In this respect, analyses of the budgetary impact could be useful but requires the use of multi-cohort models, which are more complex. The main purpose should be to assess the strategies of treatment prioritization in different populations, as well as the access to drugs in the hidden population (when they have been identified) [49]. Such data may help in prioritizing treatments.

This study demonstrated that a SMV/DCV fell below the efficiency threshold considered in our setting and is a cost-effective option in the treatment-naïve genotype-1b CHC patients with moderate fibrosis.

**Commentary**

BOC and TEL license supposed a deep change in CHC treatment. These two drugs led to a reduction in the length of treatment to 24 weeks and increase in the SVR rates in genotype-1 CHC patients, at the expense of a rise in drug adverse reactions.

The use of BOC and TEL in clinical practice was very short due to the arrival of second-generation DAAs. These drugs were more efficacious, with a better safety profile and a shorter course of treatment.

The budgetary impact that involves the new DAAs formula- 
y inclusion is a key issue that becomes more relevant during economic crisis as the current period. The high budgetary impact has carried to the establishment of prioritization programs, to find the greatest benefit. These new treatments, unlike interferon including regimes, are highly demanded by a large proportion of the patients. As a consequence, an ethic debate has been opened to select the patients who should be treated and those who would have to wait.

The search of efficient combinations, with ICERs below the cost-effectiveness threshold and lower budgetary impact, led us to consider this analysis. The SMV/DCV combination would allow extending treatment to a large number of patients, derived from the lower acquisition costs. However, the use of this therapeutic option is conditional upon efficacy data confirmation in the ongoing CTs.

The accomplishment of CEA preceding treatments license allows payers to speed up decision-making regarding treatment reimbursement and acquisition of new health-care technologies.

**Future perspective**

CHC treatment has experienced a revolution in the past few years. Nowadays, the number of therapeutic options has increased considerably, with SVR rates exceeding 90% in most patient subgroups. In the next decade, CHC treatment is likely to be different to what we already have available.

The current trends are the search of drugs combinations with a good safety profile and short-term treatment duration. It is expected to find regimes that can reduce the length of treatment to 6–8 weeks. Moreover, there are already available co-formulations of certain drugs in one single tablet with a QD administration.

The new DAAs have come along with an acquisition cost increment. As a result, there are healthcare systems that prioritize the treatment for the patients with advanced fibrosis or cirrhosis, postponing its utilization in mild-to-moderate cases. At this point, the estimated budgetary impact of CHC treatments will increase in the next years, derived from the treatment extension to patients with a less severe disease.

The acquisition costs of the currently licensed drugs are expected to fall in the short term, because of the competence among laboratories and the marketing of new upcoming drugs, as it could be observed with TEL and BOC. The treatment extension will be determined by the financial capacity to face the acquisition costs of these DAAs.

More evidence in renal impairment, co-infected, or trans- plant populations will help to establish a greater degree of accuracy on DAAs therapeutic positioning.

The establishment of patient registries can generate structures that will enable us to collect systematized data in ‘real life’ and the development of shared databases (‘big data’). These knowledge networks will help us to obtain information in specific populations where the conduction of CTs is complicated and will allow to state new drugs value in health.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. This manuscript represents the personal opinion of the authors and does not necessarily represent the views or policy of the Institutions they belong to.

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Key issues

- Second-generation direct-acting antivirals introduction represents an important therapeutic improvement for chronic hepatitis C treatment.
- Estimated incremental cost–effectiveness ratios of simeprevir/daclatasvir combination for genotype-1b patients with moderate fibrosis are situated below the cost–effectiveness threshold in comparison to boceprevir and telaprevir regimes.
- Regardless of the incremental cost–effectiveness ratio values, the financial burden considering the acquisition costs and its budgetary impact can compromise access to treatment.
- The rapid emergence of the new treatments for chronic hepatitis C makes necessary the accomplishment of a correct drug positioning by searching the most efficient therapy with the smallest budgetary impact.
- Simulation models are very interesting tools in pathologies such as chronic hepatitis C where the treatment costs are focused in the first 12 weeks and the benefits are obtained in the long term.

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