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Health Policy Analysis

Was It Worth Introducing Health Economic Evaluation of Innovative Drugs in the French Regulatory Setting? The Case of New Hepatitis C Drugs

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ABSTRACT

Objective: This paper constitutes the first attempt to draw lessons from the recent uptake of health economic evaluation of innovative drugs in the French regulatory framework. **Study Design:** Taking the example of new direct-acting antivirals against hepatitis C virus, the paper asks whether and how the cost-effectiveness (CE) opinions issued by the French National Health Authority improve the information available to support the pricing decisions. **Methods:** The analysis compares the assessment of these drugs based on three different sources: CE opinions, clinical opinions, and the published cost-utility analyses (CUA) available in the literature and identified through a systematic review. **Results:** The results show that CE opinions bring to the fore three issues prone to impact the incremental cost utility ratio and those were not

available to the decision maker through clinical opinions or published CUA: the stage of treatment initiation, the modeling of the disease progression, and the uncertainty around the efficacy rates. **Conclusions:** France has introduced the criterion of the cost per QALY gained in the pricing and regulation of innovative pharmaceuticals since 2013. Our analysis shows that the use of CUA does enhance the information available to the decision makers on the value of the treatments.

Keywords: cost-effectiveness, France, drug pricing, systematic review, chronic hepatitis C

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Introduction

Compared to other OECD countries, France only recently included health economic evaluation (HEE) as an official criterion in innovative drugs regulation. Since October 2013, pharmaceutical manufacturers have been required to submit an economic dossier to the French Health Authority (HAS) for market access [1]. The dossier presents evidence ranging from the determination of the efficiency frontier to the management of uncertainty. The CEESP (Commission d'Évaluation Économique et de Santé Publique) is in charge of the review and issues a cost-effectiveness (CE) opinion. CE opinion assesses the reliability and the methodological consistency of the dossier in reference to the HAS guidelines [2] and provides comments that aim at highlighting the salient features of the drugs' value for money. The CE opinion concludes this critical assessment by rating the limits of the dossier (namely, *réserve*) in a four-level scale, including none, mild, important, or major.

HEE is thus added to the clinical evaluation of the drugs that was already carried out within the HAS. The clinical evaluation is performed independently, in the same timeframe, by the *Commission de la Transparence* (CT). The clinical dossier details are available for clinical evidence on efficacy and adverse events. The clinical opinion concludes the review by rating the drug both in terms of its actual clinical benefit in a four-level scale from insufficient to substantial (*Service médical rendu*, SMR) and in terms of its clinical added value with respect to alternative strategies (*Amélioration du service médical rendu*, ASMR), which can be major (I), substantial (II), moderate (III), minor (IV), or absent (V).

Among the very first drugs subject to this new regulatory framework were the newest direct-acting antivirals (DAAs) against hepatitis C virus (HCV). The arrival of DAAs is considered as a paradigm shift in the HCV treatment because of highly improved efficacy rates—90% in some settings—with shorter treatment duration and fewer side effects than the existing

Conflict of interest: V. Clément is a member of the Economic and Public Health Evaluation Committee (CEESP) at the French National Health Authority (HAS). V. Raimond is employed by the HAS in the department of economic and public health evaluation. The work was done as a part of the authors' regular activity. The authors have no other interest to declare.

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1098-3015/\$36.00 - see front matter Copyright © 2019, ISPOR—The Professional Society for Health Economics and Outcomes Research. Published by Elsevier Inc.

<https://doi.org/10.1016/j.jval.2018.08.009>

strategies. However, the newest DAAs are dramatically more expensive than former ones and the issue of making their cost sustainable for national health budgets has come to the forefront of regulation policies and public debates [3–7].

In this setting, which associates high unit prices and large target population, both the importance and usefulness of HEE have been questioned. For example, Franken et al. [8], studying four European countries, showed the limited impact on the actual decisions of funding drugs yet deemed not cost-effective, and Van de Vooren et al. [9] called for prioritizing budgetary impact over CE considerations to meet high-cost drugs challenge. As the actual usefulness of HEE in the regulation of innovative drugs is debated, it is worth examining the recent French experience. Taking the example of new DAAs against HCV, the objective is to study whether and how CE opinions have contributed to improving the information provided to support pricing decisions. More precisely, the analysis aims at studying what specific information—if any—has been provided on the drugs' value thanks to the CE opinions that were available neither in the existing clinical opinions nor in the published cost-utility analyses (CUA); the latter were identified through a systematic review.

The article continues as follows: the next section presents the drugs under review and their ratings by clinical and CE opinions and reports the criteria list for the systematic review conducted. The results presented in the third section show the specific contribution of the CE opinions in documenting the value of the new DAAs. In the light of these results, the last section underlines key features of the French doctrine regarding the use of the CE opinion and discusses the issues raised by the implementation of HEE in the French regulatory setting.

Materials and Methods

The present analysis deals with all the new DAAs on which the French health authority issued opinions, namely, sofosbuvir (Sovaldi[®]), simeprevir (Olysio[®]), daclatasvir (Daklinza[®]), ledipasvir-sofosbuvir (Harvoni[®]), ombitasvir-combo (Viekirax[®]), and dasabuvir (Exviera[®]).

The purpose is to compare the information on these drugs' value provided by three different sources: CE opinions, clinical opinions, and the published CUA available in the academic literature and identified through a systematic review.

In the CE opinions, sofosbuvir incremental cost-utility ratio (ICUR) varies from €5,866 to €75,518 per quality-adjusted life year (QALY) gained depending on genotypes and interferon eligibility [10], simeprevir ICUR varies from dominated to €18,127 in genotype 1 depending on stages of treatment [11], daclatasvir ICUR varies from €14,660 to dominated depending on genotypes and interferon-eligibility [12], and ombitasvir-combo ICUR from €10,975 to €91,954 per QALY depending on fibrosis stage [13,14]. Ledipasvir+sofosbuvir ICUR was not reported as the CE opinion assigned a major *réserve*; that is, the method was not accepted [15].

The corresponding clinical opinions [16–20] reported ASMR II-III for sofosbuvir and ASMR IV for all other DAAs. The pricing decisions were taken in November 2014 (sofosbuvir), May 2015 (simeprevir and daclatasvir), June 2015 (ledipasvir+sofosbuvir), and August 2015 (ombitasvir-combo and dasabuvir).

The systematic review searched the Medline database from January 2010 to August 2015. The 5-year timeframe was aligned with the regulatory timetable in the French setting. For this reason, the literature search period was purposely stopped at the time the pricing decisions were made in order to ensure that the information was available for the pricing negotiation. Indeed the focus of the present study is on the ability of different materials to supply new and timely information to key policy and decision makers and not to provide a review of CUA for new DAAs *per se*.

The search covered peer-reviewed CUA of at least one new DAA in French and English; conference abstracts and reviews were discarded. Population, country setting, perspective, comparators, time horizon, measurement of efficacy, cost of treatment, currency and year, type of model, ICUR, and uncertainty analysis were extracted using the CHEERS checklist [21] (see [Supplementary Materials for detailed methods and main results](#)).

Twenty-one studies were eventually selected, among which 16 included sofosbuvir, 7 simeprevir, 5 ledipasvir, 1 daclatasvir, 1 ombitasvir, and 2 a new DAA as a hypothetical treatment. Eleven of the 21 were U.S. studies [22–32] and the remaining 10 were performed in Europe, of which 4 in Italy [33–36], 2 in the UK [37,38], 2 in France [39,40], 1 in Spain [41], and 1 in Switzerland [42].

CE opinions on new DAAs were then screened to identify what variables in the economic modeling were prone to significantly impact CE and consequently the pricing of the treatment. The analysis then searches whether these issues were covered either by the clinical opinions or by the published CUA.

Results

Based on CE opinions, new DAA CE appears strongly sensitive to the stage of treatment initiation, the assumptions on the disease progression, and the uncertainty around the efficacy rates.

The Uncertainty Around the Efficacy Rates

CE opinions systematically investigated how variation in the efficacy rate of new DAAs impacts the ICUR, but only a few published studies quantify the risk to observe less favorable efficacy results in current practice.

The efficacy of treatments against HCV is measured by the sustained virological response (SVR), a surrogate endpoint that corresponds to an undetectable viral load after the end of the treatment.

CE opinions on new DAAs highlighted that SVR rates were mainly based on phase II clinical trials, including a limited number of patients and that even within limited range variation; ICUR was highly sensitive to the SVR rate. For example, in genotype 1 treatment-naïve patients, a 2% reduction of daclatasvir SVR rate led to an increase of ICUR from 13% to 43% depending on fibrosis stage [12]; the variation of simeprevir SVR rate within the 95% confidence interval modifies the ICUR from €11,336 to €29,731 (vs. €14,682 in base-case) [11]; SVR rate was of the main driver of ICUR variability for ombitasvir-combo [13].

Clinical opinions also emphasized the limited data on efficacy rate. Sofosbuvir opinion acknowledged limited data for cirrhotic patients; simeprevir and daclatasvir opinions stated that new DAAs against HCV should be limited to patients who need urgent treatment because they were only evaluated in phase II trials; ledipasvir+sofosbuvir and ombitasvir-combo opinions acknowledged a better level of evidence but limited the treatment to patients with advanced disease, waiting for more treatment opportunities to be approved.

The published CUA also rested on limited clinical evidence, and data sources for the SVR rates used in the modeling were quite heterogeneous between studies. Regarding sofosbuvir, in only 7 of 16 studies all SVR rates were extracted from complete peer-reviewed publications [25,26,32,34–36,40]. In the remaining studies, at least one conference abstract or a press release from the pharmaceutical manufacturer was used as a source of SVR rate. Regarding simeprevir, daclatasvir, and ledipasvir, one study referred to an original meta-analysis [38]; all others obtained at least one SVR rate from a conference abstract or a press release. Sensitivity analysis on the SVR rates was carried out in 15 of the 21 CUA published. Results showed that with a variation of the SVR

rate ranging from 1% to 30% from the base case, the cost-effective treatment is not cost-effective anymore in 8 studies [23,24,26–28,30,34,40].

Assumptions on Disease Progression

CE opinions raised awareness on the gap between SVR achievement and health outcomes and insisted on the importance of modeling the disease progression beyond SVR to give a more realistic picture of patients' lifetime health care costs and utilities.

The HCV infection is marked by slowly progressive hepatic fibrosis with the severity of disease defined by the Metavir stage ranging from F0 (no fibrosis) to F4 (cirrhosis) and progressing through stages F1 (mild stage), F2 (moderate), and F3 (severe). Once cirrhosis has developed, long-term complications include hepatocellular carcinoma (liver cancer) and the need for liver transplantation.

The need to take into account the fibrosis stage for modeling liver disease progression after SVR was stressed in the CE opinions. One dossier (sofosbuvir) did not model any disease progression after reaching SVR, two others (simeprevir and daclatasvir) simulated a slower progression from cirrhosis to hepatocellular carcinoma after SVR, and the remaining three simulated a progression from any stage (ledipasvir+sofosbuvir, ombitasvir-combo).

Focusing on short-term biological data (i.e., SVR at 12 weeks), clinical opinions reported that the expected benefit of the new DAAs in terms of clinical outcomes was weakly documented (simeprevir) or could not be quantified (all other DAAs).

Regarding the disease progression modeling choices, the review identified three types of models: 1) patients reaching SVR do not progress anymore in the liver disease [27,29,32,33,37,39,42]; 2) patients reaching SVR continue to progress although at a slower pace from F3 [23,24,30,31] or from cirrhosis [22,28,34,38,40,41]; 3) patients reaching SVR do not progress anymore in the liver disease but are applied a lower liver-related mortality rate compared to infected patients to capture the benefit of the SVR [25,26].

When the published studies actually investigated how modeling disease progression after SVR impact the ICUR, this parameter was found to be the most influential in the deterministic sensitivity analysis [22]; it modified substantially the ICUR from 137,500 to 324,700 €/QALY gained for genotype 1 treatment-naïve patients at F3 stage and from 30,200 to 42,100 €/QALY gained for patients with cirrhosis [40] or has a significant but lower impact [28,38].

The Stage of Treatment Initiation

CE opinions stressed that the stage of treatment initiation was the main driver of new DAAs' value for money given the salient features of the epidemiology of the HCV for which the most cost-effective strategy could be postponing the treatment until disease progression has been confirmed. Modeling options used in the dossier should have been adapted to investigate the critical question.

CE opinions have discarded the analyses conducted in the DAA dossiers as they were based on an average ICUR that merged F0 to F3 fibrosis stages, failing to account for the ICUR heterogeneity between the stages [43–45]. According to the assumptions retained in the dossiers, F0–F3 patients were all cured in the same proportions and did not develop liver disease after SVR achievement; however, because only a fraction of F0 patients eventually developed a liver disease, the universal strategy that consists in treating all the patients at F0 was found potentially less cost-effective compared to a strategy where only patients \geq F2 were treated. Nevertheless, this trade-off could not be documented in

the dossiers submitted because fibrosis stages were merged, except for ledipasvir-sofosbuvir [15].

A contrasting result appeared in the early stages of the disease between a higher efficacy documented through clinical opinions and a lower CE documented through CE opinions. Nevertheless, clinical opinions have recommended putting off the treatment for patients in F0–F1 arguing that the progression rate to late stages was very slow and that these patients' therapeutic options could still be modified with the arrival of new treatments. As far as the published literature is concerned the timing of treatment initiation was barely addressed through a finely grained analysis. Only 10 studies among 21 specifically compare CE for different initiation stages, as main analysis [30,40] or in a sensitivity analysis [24–28,31,39,41]. Four studies did not differentiate at all between the fibrosis stages [23,33,37,38] and the remaining studies were based on the rather crude distinction between cirrhotic and noncirrhotic patients, which means merging F0 to F3 fibrosis stages [22,25,29,31,32,34,42].

Among the studies that modeled treatment initiation at different stages, ICUR was always found higher in earlier stages; for instance, it raises from \$14,159/QALY gained at cirrhosis to \$51,344 in F0 [26]. The universal strategy was shown to be more costly and to provide more QALYs than treating in later stages; however, the ICUR varies widely among studies ranging from cost-effectiveness with \$15,709/QALYs gained [30] to \$103,500/QALY and \$321,300/QALY [40].

Discussion

In the light of these results, three underlying issues about the uptake of HEE and its implications for pricing and coverage decisions in France are worth discussing.

First, the analysis allows underlining key features of the French doctrine regarding the use of the CE opinions. CE opinions are used as an official criterion only in the pricing negotiations between the pharmaceutical manufacturer and the Pricing Committee [46] and are not taken into account in the reimbursement and listing decisions. Moreover, no CE threshold (CET) is used in the French setting. A necessary condition for the pharmaceutical manufacturers to benefit from the European reference prices is that efficiency could be established on the basis of the economic dossier when ASMR I, II, or III is obtained. The CE opinion could indicate that it is not the case by ranking the dossier with a "major" reserve grade that points out that the method or the model is flawed or that the level of uncertainty removes all relevance from the quantitative results, as illustrated by ledipasvir+sofosbuvir. Hence, from a purely regulatory perspective, the methodology and its consistency appear more important than the ICUR level. CE opinions pay particular attention to the factors and variables impacting the uncertainty so as to provide a basis to negotiate prices and use, which could be subgroups of patients with different CE or the time to initiate the treatment as exemplified by the results on new DAAs. The question raised is then whether moving toward the uptake of CE opinions in the decisions of what to fund and the definition of a CET would improve the usefulness of HEE to tackle with high-cost treatments in the French setting. Studying countries where these conditions are met, Franken et al. show that the ways have generally been found to avoid refusing to fund high-cost drugs on CE grounds. The paper concludes that HEE had limited impact on the listing decisions but eventually helped in the price negotiations in particular by determining subgroups of patients who benefit most, which fully corresponds with the role devoted to the CE opinions in the French setting. Hence, the comparison with the results of Franken et al. could lead to arguing that French-specific features

regarding the implementation of HEE do not seem to impact its usefulness. More comparative case studies are needed.

The second issue concerns the compatibility between the clinical and the CE opinions. A distinctive feature of the French innovative drugs pricing regulation system is that it is based on two approaches for assessing the value added by the drugs, namely, the cost per QALY gained and the ASMR ranking. This twofold evaluation is debated and the need to converge toward a single opinion has been underlined by recent public reports [47,48]. The present study shows that the criteria could actually complement each other: the clinical opinions' recommendation to postpone treatment initiation to F2 fibrosis stage was indeed reflected in higher ICUR for earlier stages. Drummond et al. came to a similar conclusion in the case of anticancer drugs showing that a superior ASMR score was associated with higher QALYs gained [49]. Nevertheless, from the perspective of priority settings, the existence of twofold assessment criteria means that the cost per QALY gained is to be weighted by the level of ASMR reached. The latter is prone to introduce considerations related to the severity of the disease or to the line of treatment, and more generally to the repartition between the quality of life and life expectancy within QALYs gained in a break with the standard principle of cost-utility analysis [50,51]. Indeed the ASMR criterion discriminates quality of life improvement (more often associated with ASMR III or IV) and survival benefit (more often associated with ASMR I or II), whereas the QALY does not. In this perspective, the coexistence of two distinct criteria for assessing the value of the drug might turn to be highly questionable to the extent that it could impede the transparency of the process for prioritization.

The last issue questions the usefulness of CE opinions against the threat to the sustainability of the health care budget because of high-cost treatments. As illustrated by HCV drugs, affordability has become a major concern in health care [6,7]. The emphasis on the budgetary impact had taken two different forms in the French regulatory setting. First, regarding new DAAs, the French Ministry of Health has taken the unusual decision of capping the overall yearly social security expenses for funding hepatitis C drugs and taxing the industry on the revenue exceeding the cap [52]. Second, the latest agreement between the Pricing Committee and the pharmaceuticals industry made the budget impact analysis compulsory in the market access [53,54]. In this context, the question of which should come first between CUA and budget impact analysis may arise as supported by Van de Vooren et al. calling for a block contract between the industry and the regulator where the main decision from the latter would be to define what subgroup to treat; the global budget is then estimated from the cost savings provided by the new drugs [9]. As relevant as it is, this proposal sounds like a step backward in the French setting, where CE considerations were discarded from the pricing regulation process until recently. Moreover, the present analysis shows that the ICUR provides precisely pivotal information on the trade-off between who should be treated and the expected health care costs avoided, indicating that CE opinions remain the necessary first step to implement pricing regulation.

Several limitations of the study should be acknowledged. First, the analysis focuses on a single therapeutic class and therefore could not be considered as representative of the dossiers submitted to the CEESP especially because HCV drugs challenge is related to pay for curing a large population of a slowly progressive disease and methodological issues might differ from treatments of chronic diseases, anticancer drugs, or orphan drugs. Nevertheless, major regulatory issues were at stakes with new DAAs, which makes this case-study paradigmatic so as to analyze the implications of the uptake of CE opinions in the French setting.

Next, the DAAs' dossiers were submitted at the outset of the CEESP review process when all the stakeholders were in the learning curve. CE opinions probably evolved with the level of

expertise of the CEESP and of the laboratories that slightly increased since this time. The present analysis provides an example of this ongoing process: the assumptions on disease progression have indeed evolved between sovaldi dossier and the subsequent sovaldi+ledispavir dossier. Moreover, CE opinions may still undergo changes to address new issues like reassessment with real-life data or the development of treatment staging, for example. There is no doubt that updated health policy analysis will be needed over time.

Finally, it should be emphasized that the present analysis is not intended to quantify the impact of CE opinions on the price actually paid by the health system for the drug partly because the public price does not match up to its contractual price as price-volume agreements or rebates arrangements are not disclosed, and partly because pricing agreements include other considerations than CE such as reference pricing or industrial considerations, which may require a quantitative approach based on a longer CE opinions experience.

Conclusions

France has introduced the criterion of the cost per QALY gained in the pricing and regulation of innovative pharmaceuticals since 2013. Taking the example of the new DAAs against HCV, the analysis shows that the use of CUA does enhance the information available to the decision makers on the value of the treatments.

Acknowledgments

The authors want to thank S. Affinito for his participation in the startup of the project, M. Cecchin and S. Lascols for their support in the literature search, and J.M. Josselin and C. Rumeau-Pichon for their comments on an earlier version of the paper. The two authors equally contributed to the analysis and the writing of the paper and are solely responsible for the final draft of the paper.

Supplemental Materials

Supplemental material associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2018.08.009>.

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