Evolocumab and alirocumab: exploring original procurement models to manage the reimbursement of these innovative treatments

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Abstract. Background: PCSK9 inhibitors (evolocumab and alirocumab) pose a challenge of sustainability because the potential patients are extremely numerous and the budget impact at the drugs’ full price would be prohibitive. We have studied the reimbursability of these agents by constructing a series of price-volume simulations that used a model previously employed for sofosbuvir. Methods: Our price-volume model is based on the following parameters: i) total patients candidate to the treatment; ii) patients actually treated; iii) treatment full cost per patient; iv) estimated nationwide budget impact in the absence of any price-volume intervention; v) price-halving population (PHP), which is the main model parameter. Treated patients ranged from 30,000 to 100,000. The full nominal yearly cost per patient was set at 10,000 €. Results: In 9 price-volume simulations (testing three values of PHP at 25,000 or 50,000 or 100,000 patients), the total national expenditure varied from 204 to 721 million. In the least expensive scenario (PHP = 25,000 patients), the expenditure ranged from 204 to 338 million € while the average treatment cost per year was 3,382 €. At more than 100,000 treated patients, the treatment cost reduced to 626 €. On the other hand, the scenarios based on PHP = 50,000 and PHP = 100,000 patients were very unlikely to be acceptable for national health systems. Conclusions: Our study offered a pattern of different scenarios among which some national health systems in Europe could select the “true” decision on PCSK9 inhibitors. This decision is expected to be made over the next few months.

Introduction

In the field of pharmaceutical innovation, the newest interferon-free treatments for hepatitis C (or direct acting antivirals, DAAs) represent an unprecedented case in terms of sustainability because in most countries the number of potential patients is extremely high and the consequent potential budget impact per year is of the order of billion dollars or billion EUR [1, 2]. To manage this issue, all countries where DAAs are available have restricted the reimbursement of these agents to patients with advanced disease and have consequently decided not to reimburse them for patients with mild disease. Although some local experiences have been tried to ensure reimbursement also to patients with mild disease [3]. To our knowledge, none of these experiences has thus far been successful.

It is agreed that price rebates are the only solution to extend the reimbursement of these agents to an enlarged population of patients. However, drug manufacturers have always refused to consider price rebates that directly reduce the nominal price, and so the only solution has been represented by price-volume agreements set at the national level [4, 5]. These agreements determine a progressive price reduction as more and more patients are treated; hence, they prove to be particularly suitable for cases where the drug price is high and the population is large. The pattern of price decay with volume has generally a purely empirical nature, but a theoretical basis would be needed.

PCSK9 inhibitors (evolocumab and alirocumab), which have recently been approved by both FDA and EMA, pose a similar question because the number of potential patients is high and the budget impact would be prohibitive if calculated on the basis of the drugs’ full nominal price [6]. In a previous report, we simulated 6 different scenarios for managing the price-volume agreement of sofosbuvir in the Italian national health care system [5].
The agreement is now routinely used nationwide to manage all reimbursements of the drug and, more importantly, has led to marked price rebates as more and more patients are given the treatment.

In the present study, we have studied the case of PCSK9 inhibitors and, for this purpose, we have constructed a series of national price-volume simulations based on the same model previously employed for sofosbuvir \[4, 5\] and focused this time on PCSK9 inhibitors. The aim of our study was to offer a pattern of different scenarios among which, in the near future, our national health service could select the “true” decision on PCSK9 inhibitors. This decision is expected to be made over the next few months.

### Methods

Our price-volume model \[4, 5\], published in 2014 for use with sofosbuvir [5], includes the following information (Table 1): i) total number of patients candidate to the treatment (totPT); ii) number of patients actually treated (Npt); iii) full price per patient (fPRICE); iii) estimate of the nationwide budget impact in the absence of any price-volume intervention (calculated as fPRICE × Npt). Although the decay is exponential, applying a logarithmic transformation to the y-axis data converts this curve into a straight line; hence, the knowledge of only two points permits to determine a full model parameterization.

Making the price-volume assessment as objective as possible is a difficult task. In the simulations developed according to the model, the “best” scenario for the payer is the one that maximizes the cost per patient. Of course, seeking a compromise between these two extremes requires the identification of some objective determinants that foster this “compromise” either in favor of the payer or in favor of the manufacturer.

A tentative list of the main determinants that should favor the payer and suggest a rapid price decay with volume includes: a) a poor cost-effectiveness of the treatment (when evaluated at its full price); b) a low production cost of the drug; c) a very large size of the population of treatable patients; d) the expected expenditure at full price for the drug represents a “substantial” proportion of the overall pharmaceutical expenditure. On the contrary, determinants favoring the manufacturer and suggesting a slow price decay with volume include: a) a favorable cost-effectiveness of the treatment (when evaluated at its full price); b) a high production cost of the drug; c) a relatively small size of the population of treatable patients; d) the expected expenditure at full price for the drug does not represent a “substantial” proportion of the overall pharmaceutical expenditure.

To develop our simulations according to Equation 1, the following assumptions regarding PCSK9 inhibitors were made: a) the yearly cost of PCSK9 inhibitors at full price is 10,000 EUR per patient [6]; b) the maximum usage of PCSK9 inhibitors is set at the yearly value of defined daily doses employed for ezetimibe in 2014 (which is ~ 110 million according to an official report of our Medicines Agency [7]); c) three values of PHP (25,000 or 50,000 or 100,000 patients) are assessed in the three simulations, respectively; d) each of the simulations examines three scenarios in which the total number of treated patients is 30,000, 50,000, and 100,000, respectively.

Finally, the average treatment cost across all treated patients was calculated according to the following equation (which simply represents the integral of Equation 1 between x = 0 and x = totPTS):

\[
\text{Average treatment cost} = (\text{fPRICE} - \text{fPRICE}_{\text{last}}) \times (\text{PHP} \times 0.693) / \text{totPTS} \quad (\text{Equation 2})
\]

where \text{fPRICE}_{\text{last}} is the treatment cost estimated at \text{totPTS}.

### Results
Overall, a total of 9 simulations were carried out according to our analysis (Table 2) (Figure 1). In these simulations, the total national expenditure varies widely (from 204 to 721 million €) depending on the specific scenario. The full nominal yearly cost per patient is set at 10,000 €. Regarding the “true” average yearly cost per patient (adjusted according to the price-volume equation), its value ranges from 3,382 to 9,029 €.

Among the data shown in Table 1, the values of predicted nationwide expenditure represent, in our view, the most informative parameter from the point of view of the payer. If one considers the least expensive scenarios (i.e., those based on PHP = 25,000 patients), the nationwide expenditure calculated by our model ranges from 204 million € to 338 million € (corresponding to a number of treated patients ranging from 30,000 to 100,000). In particular, in the scenario of 338 million € of total expenditure = 338 million € assuming 100,000 treated patients and PHP = 25,000 patients, the average treatment cost per patient per year is 3,382 €, but – at more than 100,000 treated patients – this treatment cost reduces to less than 626 € (with a very substantial percent discount of 93.7%) (Figure 1).

In our view, particularly if historic reimbursement decisions aimed at funding new treatments in Italy are taken as a benchmark, the scenarios based on PHP = 50,000 patients and PHP = 100,000 patients are very unlikely to be accepted by our national health system.

**Discussion**

In the past, price-volume agreements have been applied on empirical basis, i.e., in the absence of any quantitative rule. The Italian experience with sofosbuvir and the subsequent papers focused on this price-volume agreement have been the first attempt to generate a conceptual framework in this field. Interestingly enough, three parameters (PHP, fPRICE, totNP) were found to ensure an adequate modelling of the price-volume relationship.

In handling the issue of drug pricing, critical cases similar to that of sofosbuvir are likely to occur quite frequently, especially in areas of pharmacotherapy such as oncology, cardiovascular targeted drugs, ophthalmological targeted agents, etc. In this context, the availability of a rational model is a useful prerequisite to ensure that price-volume decisions made for different agents are not purely empirical, but tend to share the same rationale or the same operational strategy.

Our study investigated the modeling of PCSK9 inhibitors (evolocumab and alirocumab).
rocumab), which are considered the most challenging reimbursement decision that payers are expected to face in the next few years. The recent papers by Shrank et al. [8] and by Persson and Jönsson [9] confirm the view that pharmaceutical firms are unwilling to accept rebates in nominal prices for these agents. Hence, competitive tenders (usually leading to public price offers) are expected to be unsuccessful in determining price rebates in this therapeutic area.

On the other hand, pharmaceutical manufacturers are thought to be more likely to accept agreements based on confidential price rebates [8, 9] particularly when the price negotiation is directly made with the negotiation organism of a national health system (as in the case of Italy and France). In this context, the present article has offered a series of simulation scenarios that, in our view, could be useful to decision-makers in the near future to decide which price-volume agreement can be suitable for these innovative treatments. The main advantage in using the models described herein is that these models have not a purely empirical nature, but incorporate an original conceptual framework aimed at introducing a rationale into these price-volume agreements.

**Conflict of interest**

None declared.

**References**


