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Systematic Review

Budgetary Impact and Cost Drivers of Drugs for Rare and Ultrarare Diseases

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ABSTRACT

Objectives: To review recent studies reporting health care expenditures (budgetary impact) for orphan medicinal products (OMPs) in Europe and to contribute to our understanding of the cost drivers of nononcological OMPs by means of an empirical analysis in Germany. **Methods:** A systematic search for relevant studies on rare diseases was conducted in PubMed and Embase (until December 2016). In addition, annual treatment costs of nononcological OMPs in Germany were analyzed with respect to five explanatory variables: total prevalence of disease, prevalence with added benefit, availability of alternative treatments for the same indication, extent/probability of treatment benefit, and evidence for a treatment effect on mortality. **Results:** A total of nine studies with specific estimates of the budget impact of OMPs for a total of 11 countries were identified; one study addressed specifically ultrarare diseases. Annual per-capita spending for OMPs ranges from €1.32 in Latvia to €16 in France. Per-patient annual treatment costs vary between €27,811 and €1,647,627 in Germany. On the basis of the German data set, the regression analysis shows that log prevalence has a significant inverse relationship with log annual treatment cost. In this model, doubling the prevalence leads to a 43% decrease in annual treatment cost. **Conclusions:** Despite per-patient annual treatment costs ranging up to several hundreds of thousands of euros for some OMPs, per-capita spending for OMPs is relatively small. In this study an inverse relationship between prevalence and annual treatment costs was found.

Keywords: budgetary impact, drug prices, orphan medicinal products, prevalence, rare diseases, ultrarare diseases.

Introduction

In many jurisdictions, including the United States, the European Union (EU), Japan, and Australia, legislation has been adopted to encourage the development of treatments for rare or "orphan" diseases. Under this legislation, developers and manufacturers of so-called orphan drugs used to treat orphan diseases benefit from a range of incentives, including reduced or waived licensing fees, extended market exclusivity periods and, in the United States and Japan, tax relief on development costs [1–3].

The introduction of regulation for rare disorders has contributed to the rise of research and development efforts, leading to increasing availability of effective treatments for rare disorders [4]. From the perspective of the biopharmaceutical industry, orphan medicinal products (OMPs) are now attractive investment opportunities [5–7]. At the same time, however, in many cases the use of drugs for rare disorders has been associated with high annual acquisition costs per patient, and "the five most expensive drugs in the world" [8] all happen to be medications for ultrarare diseases (URDs).

Fixed costs of research and development are largely independent from sales volume or for that matter from the very small number of patients affected with a rare disorder. Consequently, one should expect an inverse correlation between drug acquisition costs per patient and the prevalence of the target condition (in line with, e.g., [9]).

Against this background, concerns have been raised that drugs for orphan disorders "may impose substantial increasing costs to the healthcare system" [10], to the point that these costs may become "unsustainable, even for health services that have met them hitherto" [4]. Many of the technologies in question do not meet broadly used benchmarks for cost-effectiveness, for example, incremental costs per quality-adjusted life-year gained of €50,000 (e.g., [11–13]), and sometimes cost-effectiveness data

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are not available at all (cf. [14]). As a result, recent debate has focused on the appropriateness and usefulness of conventional cost-effectiveness analysis as a tool to determine the "value for money" offered by OMPs [13,15–17]. Accordingly, in many jurisdictions OMPs are exempted from formal health economic analysis (e.g., in some cases in the Netherlands), follow specific processes, or receive positive reimbursement decisions despite indications of costs per quality-adjusted life-year higher than deemed acceptable in other areas (e.g., [18–21]).

As the prevalence of conditions displays a continuous pattern, attempts to separate "orphan" and "ultra-orphan" from "normal" conditions are somewhat arbitrary exercises. Nevertheless, orphan disorders have been defined by the US and EU legislations. In the United States, these are diseases with a prevalence of fewer than 200,000 affected persons; in the EU, prevalence must be fewer than 5 per 10,000 (or $<0.05\%$) of the population.

The National Institute for Health and Care Excellence in the United Kingdom introduced a definition of ultra-orphan drugs that it applied to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons initially in 2005, and then subsequently less than 100 patients in England in the recently updated Highly Specialised Technologies appraisal process in 2013. Similarly, the recent EU Clinical Trials Directive [22] defined URDs as "severe, debilitating and often life-threatening diseases affecting no more than one person in 50 000."

In Australia, the Pharmaceutical Benefits Advisory Committee often considers URD drugs within the context of the Life Saving Drugs Program [23]. It remains to be seen whether such programs provide sufficient incentives to develop products and reverse possible trends toward an increasing number of companies focusing on more prevalent orphans and fewer in the "very rare" category [24].

The objective of the present article was 1) to review recent studies reporting health care expenditures (budgetary impact) for drugs for orphan diseases (including URDs) in Europe and 2) to contribute to our understanding of the drivers of acquisition costs of OMPs by means of an empirical analysis. Specifically, we searched for variables explaining costs of OMPs as negotiated between manufacturers and representatives of the German statutory health insurance. We particularly aimed at confirming the theoretical relationship between disease prevalence and drug costs empirically. This should be of interest given the lack of transparency of and very limited research on the pricing of OMPs [25,26] and, in particular, drugs for URDs.

For the cost driver analysis we focused on the German market, which is the largest European market in terms of pharmaceutical production and sales [27]. Specifically, we analyzed OMPs that had completed an early benefit assessment in Germany (see Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.10.015 for details of the benefit assessment process in Germany). We chose to focus on nononcological diseases because our dependent variable, which is annual treatment costs, does not fit oncology drugs well because the application of oncology drugs is often based on a limited number of cycles or time to treatment progression.

Methods

Budgetary Impact of OMPs

We conducted a systematic search for relevant full-text articles on rare diseases (including URDs) in PubMed and Embase (until December 2016), using the search algorithm "orphan drugs AND (budget impact OR spending)." Studies with data from outside Europe and those reporting individual-level but not population-level cost data were excluded. When estimates were reported over a multiyear period, we took the latest one.

Local currencies were converted into euros on the basis of the exchange rate at the time of the study in question. To calculate per-capita cost, we used population data of the study year in question from the World Bank [28].

Drivers of Cost per Patient for OMPs

Data sources

We included all pharmaceuticals that were classified as OMPs by the Federal Joint Committee, had completed an early benefit assessment by the end of 2016, and were not withdrawn from the German market. Drugs had to be approved by the European Commission in a nononcological indication. We analyzed annual treatment costs with respect to five explanatory variables: total prevalence of the disease (continuous), prevalence with added benefit (continuous), extent/probability of benefit (discrete), effect on mortality (discrete), and availability of alternative treatments for the same indication (discrete). Variables are explained in the following sections.

Annual treatment costs. Information on annual treatment costs before price negotiation between a manufacturer and the National Association of the Statutory Health Insurance Funds was obtained from the official resolution document issued by the German decision-making body, the Joint Federal Committee (or *Gemeinsamer Bundesausschuss* [G-BA]). If unavailable from this source, data were retrieved from assessments by the German health technology assessment agency, the Institute for Quality and Efficiency in Health Care (cf. also Appendix in Supplemental Materials). In cases in which several dosing regimens were reported (e.g., on the basis of age or weight), we took the average of the upper and lower bounds of annual treatment costs. In a sensitivity analysis representing a conservative scenario, we used upper bounds only.

To arrive at the annual treatment cost after price negotiation between a manufacturer and the National Association of the Statutory Health Insurance Funds, we determined the negotiated rebate as listed in the Lauer-Taxe® as a percentage of the manufacturer's asking price and applied this percentage to the annual treatment cost before negotiation. For drugs for which negotiation results were unavailable (e.g., because negotiations were still ongoing or prices were being set by the arbitration body), we applied the average rebate of drugs with available information.

Prevalence. When possible, we used prevalence data gathered by Orphanet [29] or else the assessment reports by the European Medicines Agency. For OMPs with an indication for more than one rare disease (i.e., pasireotide and riociguat), we determined the sum of prevalence rates.

In addition to total prevalence, we included the size of the population expected to have an added benefit in the German statutory health insurance system. The size of the population with expected benefit is supposed to be smaller than the total prevalence because it takes into consideration, among others, contraindications, age restrictions, and lack of access to treatment, for example, because patients may not be detected. For example, in Germany less than 200 patients with type 1 Gaucher disease were treated in 2009 [30], whereas total prevalence data [31] suggest the patient population to be about 800. Nevertheless, estimates on the population size with expected benefit are subject to large uncertainty and therefore still justify a concomitant consideration of total prevalence estimates. As a source of the population size with expected benefit, we used estimates by