REVIEW ARTICLE

Health Economic Assessment: Applications, Rationale, Methodology and Common Mistakes

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Abstract Economic assessments are useful to compare the effects and costs of different health interventions, with the purpose to determine the best alternative for resource distribution in health institutions. To this end, it is highly important for the economic analysis to be consistent with the context where it is carried out, and to follow the established methodology on the subject. Using as an example a recently published cost-effectiveness analysis that compares panitumumab with bevacizumab and cetuximab in patients with metastatic colorectal cancer in Mexico, we will show how to develop a transparent, fair, and useful economic assessment for decision makers. (creativecommons.org/licenses/by-nc-nd/4.0/).

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INTRODUCTION

Economic assessments of new treatments are primarily intended to serve as a tool for decision makers and to advise them in establishing the best alternative for resource distribution. To accomplish this goal, as well as to arrive to valid conclusions, following an established methodology is required, especially focusing on the context where the analysis takes place. Otherwise, what would be the use of an economic assessment? Based on the article by Vargas, et al. entitled “Cost-effectiveness analysis of panitumumab + FOLFOX in RAS-WT mCRC” published in the *Gaceta Mexicana de Oncología*¹, the present article outlines the fundamentals to conduct and analyze a health economic assessment, describes mistakes to be avoided, and offers tools for findings to be interpreted and validity of conclusions to be evaluated.

The fundamentals of new treatments economic assessment can be summarized in six simple points:

- Establishing a clear, precise research question;
- The research must have objectives that are consistent with the guidelines established within the context where the drugs are assessed;
- The type of economic assessment (cost-effectiveness or cost-minimization) should be justified by available evidence from quality clinical trials;
- The clinical trials used to support the effectiveness of all treatments should correspond to the study population;
- The costs used in the study should correspond to the perspective of the study, to the usual costs of a patient with a given disease, as well as to the medication, including costs of administration, hospitalization, follow-up and treatment of adverse effects; and

The sources of data on efficacy, costs and assumptions should be clearly cited and available to assessors².

Each one of these points will be next examined in the context of the economic assessments carried out by Vargas, et al. in order to determine the methodological validity and the results of the two presented analyses: a cost-effectiveness analysis comparing bevacizumab with panitumumab and a cost-minimization analysis where cetuximab is compared with panitumumab.

ESTABLISHING A CLEAR, PRECISE RESEARCH QUESTION

The research question is essential in order to focus the investigation and define its scope. In the analyzed article¹, the research question clearly establishes the context: “Does the use of panitumumab + FOLFOX as first-line treatment in patients with wild type (WT) RAS metastatic colorectal cancer (mCRC) have an inferior cost-effectiveness ratio average versus bevacizumab + FOLFOX, as assessed from the perspective of public health institutions in Mexico?”. With this question, the treatments under investigation (panitumumab and bevacizumab), the population of interest (patients with WT RAS mCRC) and the specific context (public health institutions in Mexico) are known.

For the performance of any economic assessment study, and in order for it to meet its purpose, i.e. to guide the de-

cision maker, the assessing entity acceptance criteria, which are determined by the context itself, should be applied. In particular, for public sector institutions in Mexico, these criteria are dictated by the General Public Health Council (CSG - Consejo de Salubridad General), which is the body responsible for assessment and inclusion of new technologies into the Basic Formulary and Medication Catalogue^{3,13}.

THE RESEARCH MUST HAVE OBJECTIVES THAT ARE CONSISTENT WITH THE GUIDELINES ESTABLISHED WITHIN THE CONTEXT WHERE THE DRUGS ARE BEING ASSESSED

Presentation of results

The Guidelines for the Conduction of Economic Assessment Studies for the Basic Formulary and Catalogue of Supplies of the Health Sector in Mexico Update² indicate that the presentation of a cost-effectiveness analysis (CEA) is “indispensable”, with efficacy results expressed in “natural units such as, for example, life-years gained” (p. 34), and final results expressed as “incremental cost per additional efficacy unit” (p. 20). This methodology is, in addition, consistent with other reference institutions in health economic assessment at the international level^{4,5}. However, Vargas, et al. present the results as a “cost-effectiveness average” measurement, which is not a commonly employed cost-effectiveness measure and, given the context, it doesn’t allow for the decision maker to clearly know the incremental cost per efficacy unit.

The CSG establishes cost-effectiveness threshold at one GDP per capita, which is equal to MXP \$ 120,214.18^{6,7}.

Gross domestic product per capita is calculated with the following formula:

$$\frac{\text{GDP}_{\text{Mexico}}}{\text{Population}_{\text{Mexico}}}$$

Using Vargas, et al. own data on costs and effectiveness¹, the calculation of the incremental cost-effectiveness ratio (ICER) for panitumumab in comparison with bevacizumab would be:

$$\text{ICER} = \frac{(\text{Treatment A Cost} - \text{Treatment B Cost})}{(\text{Treatment A Effectiveness} - \text{Treatment B Effectiveness})}$$

$$\text{ICER} = \frac{(\$1,048,009.42 - \$872,201.70)}{(3.47 \text{ years} - 2.80 \text{ years})} = \$262,399.5$$

According to this result, panitumumab ICER is above the cost-effectiveness threshold established for Mexico. Notwithstanding, the result presented by the author omits this information and appears to suggest the opposite by indicating that panitumumab has a lower “cost-effectiveness average ratio” than bevacizumab.

The use of ICER implies acceptance by the government to pay an additional amount established for medications that demonstrate higher effectiveness. In contrast, the use of the cost-effectiveness average ratio implies that treatments with higher effectiveness should have the same cost per life-year gained than the other compared medications, which has at least three methodological flaws:

- It implies that new products require having the same cost per life-year gained than generic products.
- Each disease is likely to have a different life-year cost, since there is no consensus on life-year gained average cost standardization.
- This methodology is used to compare treatments against “no intervention”⁸.

To be correctly employed, an analysis of panitumumab versus the no intervention alternative should be included.

Cost-effectiveness analysis methodology should be consistent with the context and the guidelines where the study is developed. In this case the methodology employed by Vargas, et al. to justify panitumumab cost-effectiveness versus bevacizumab does not correspond to standard methodology, which can lead to wrong decision making in resource optimization.

Data on resection

It is important for sources of the data used in the economic model to be consistent with the context where it is developed. Vargas, et al. rely on data of the PEAK clinical trial to model the compared treatments efficacy. However, to model the resection, the investigators chose to rely on data of an expert panel to determine the resection rate and intervention rate of success. The CSG Guidelines clearly state: “In no case will be expert opinions able to replace proven scientific evidence”² (p. 21). The data on resection attempt and rate of success of Vargas’ analysis, 11 and 80%, respectively, for panitumumab, and 22.2 and 71%, respectively, for bevacizumab, not only considerably differ from the PEAK trial data (13.6 and 66.7% vs. 11 and 77.8%, respectively)⁹, but also favor panitumumab by adding the costs of unsuccessful surgery to bevacizumab-treated patients.

It is important to emphasize that actually, these data cited by Vargas, et al. do not come directly from the PEAK analysis report⁹, but from an economic assessment published in 2014 that was carried out by the PEAK trial sponsors, who had access to patient-level data¹⁰.

It is explained that two additional scenarios were used to determine with more certainty the validity of the results presented with the base case: “with the first one assuming the same percentages reported in the PEAK trial (13.6% for resection attempt and 66.7% for rate of success with panitumumab and 11% for resection and 77.8% for success with bevacizumab), and the second assuming no metastatic site resection is performed (0% of attempts)”¹ (p. 253).

However, the results of these are not presented in the article, casting more doubt on the transparency and validity of the study. In this example, unpublished data are used that justify adding more surgeries with less effectiveness to bevacizumab patients, which increases the cost of treatment for these patients, thus favoring panitumumab.

Here, the recommendation would be using published data, and justify any variable value change in order for results to be replicable.

THE TYPE OF ECONOMIC ASSESSMENT (COST-EFFECTIVENESS OR COST-MINIMIZATION) SHOULD BE JUSTIFIED BY AVAILABLE EVIDENCE FROM RANDOMIZED CLINICAL TRIALS AT LEAST MEETING MINIMUM QUALITY REQUIREMENTS (JADAD SCALE OR CONSORT)

The researchers should choose a type of economic assessment according to available clinical information on the different comparators included in the evaluation. In the Mexican context, researchers usually choose between a cost-effectiveness analysis when the treatments to be compared have different efficacy, and a cost-minimization analysis only in cases where there is proof that there is no effectiveness difference between the drugs to be compared².

The cost-effectiveness analysis is based on overall survival data of the PEAK trial, which compared panitumumab and bevacizumab (41.3 vs. 28.9 months, respectively). The clinical trial is completed with a statistical analysis of results to determine the 95% confidence intervals (CI) and, by this means, the certainty of the trial results. In the case of the PEAK trial, data are not statistically significant (95% CI: 0.39-1.02; $p = 0.058$)⁴. In addition, the CI is so broad that it does not allow for conclusions on the intervention effect to be extracted.

THE CLINICAL TRIALS USED TO SUPPORT THE EFFECTIVENESS OF ALL TREATMENTS SHOULD CORRESPOND TO THE STUDY POPULATION

Clinical trials are intended to determine the efficacy of a treatment in a specific population. For this reason, it is very important for the population where the economic assessment is carried out to correspond to this same population. In the reviewed article¹, the study is carried out in patients with KRAS-WT mCRC on first-line treatment. The cost-minimization analysis between panitumumab and cetuximab is based on the assumption that both drugs have the same efficacy in the study population and, consequently, only the costs are compared, without effectiveness being considered. The author cites as clinical evidence a study in RAS-WT population on third-line therapy (the ASPECCT trial¹¹), which is not valid to demonstrate panitumumab and cetuximab equivalence at first-line, and since a comparison merely based on costs is not justified, no valid conclusions can therefore be obtained from this analysis. In order for valid conclusions on the cost-effectiveness of these products to be presented, an analysis is required on the clinical benefits of the medications, and not only on their costs, as well as sensitivity analyses to be included to assess the impact of uncertainty on the results.

THE COSTS USED IN THE STUDY SHOULD CORRESPOND TO THE USUAL COSTS OF A PATIENT WITH THE DISEASE OF INTEREST, AS WELL AS TO THE MEDICATION, INCLUDING COSTS OF ADMINISTRATION, HOSPITALIZATION, OUTPATIENT CONSULTATIONS, AND TREATMENT OF ADVERSE EVENTS

In order for it to really be a tool to support decisions, the economic assessment and treatment algorithm of the average patient should adhere as much as possible to the reality where the model is developed. In addition to the aforementioned methodological points, there is an inconsistency between the two economic analyses presented in the article by Vargas, et al.¹ that turns out favoring panitumumab cost estimate. In the cost-effectiveness analysis of panitumumab with bevacizumab, an average patient weight of 67 kg was used based on an article¹² where patients with cancer were assessed at the Hospital General de México. Conversely to this data, Vargas, et al. changed patient weight to 65 kg in the comparison with cetuximab. The panitumumab dose is indicated in mg/kg, as with bevacizumab, while cetuximab dose is indicated in mg/m². The subtle patient weight change allows for one less panitumumab vial to be used, which decreases its treatment cost, thus generating a bias in the presented results.

THE SOURCES OF DATA ON EFFICACY, COSTS, AND ASSUMPTIONS SHOULD BE CLEARLY CITED AND BE ACCESSIBLE TO ASSESSORS

The validity of an economic assessment is based on the quality and certainty of the employed information. For this reason, when developing a study it is important to make sure that the data are consistent with the context they are applied to, and that the sources of the analysis key data (efficacy and costs) are accessible in order to validate the model. As the authors of the article note¹: “The performance of a pharmacoeconomic analysis that turns out being relevant to the national context is determined by the quality of the information it feeds on and by the consistency of the assumptions employed in the assessment model with clinical practice in Mexico”¹ (p. 253). In spite of this accurate statement, the same authors include non-supported assumptions or fail to mention results that are critical to the results interpretation.

When the article by Vargas, et al.¹ and the sources referred to justify the assumptions for costs and efficacy of the included treatments were reviewed in detail, an economic assessment was found of the PEAK clinical trial of panitumumab compared with bevacizumab⁹, the results of which were used as the basis for the economic assessment¹⁰. Economic models adaptation for different contexts is common practice. However, not citing the original document is considered a serious offense within the scientific community.

Overall, there is a lack of transparency in cost assumptions: How was the cost of metastasis resection estimated? Why does the range of the sensitivity analysis for this variable go from -20 to +50%? Why is the cycle number upper

range 21.65, and where does this figure come from? Why is comparator total treatment cost not reported in the cost-effectiveness analysis including administration and follow-up? All these data should be more clearly presented in order for the reader to be able to draw his/her own conclusions.

In spite of having a previously published economic assessment, these doubts are not clarified. On the contrary, some of the explained and most conservative variables in the model by Graham, et al. do not correspond to those used by Vargas, et al., where data sources are not explained. For example, the average number of treatment cycles corresponds to the average time the patient is on progression-free survival. Using parametric modeling, Graham, et al. explain that the Weibull distribution was used to define the time average the patient spends on progression-free status (19.42 cycles with panitumumab and 14.10 with bevacizumab)¹⁰. Vargas, et al. use the same number of cycles for bevacizumab (14.10), but reduce the cycles of panitumumab treatment to 18.20¹. In both cases, the provenance of these data is not explained.

CONCLUSION

Economic assessment is a highly useful tool to compare different health technologies and to support decision makers on the use of more cost-effective treatments. Therefore, it is important to follow published methodologies that have been gradually defined with this discipline's growth. In addition to clearly explaining the study population, the technologies to be compared and the sources of data, it is important for data to be transparently used in order to prevent bias in the results.

The economic assessments of panitumumab versus bevacizumab and cetuximab presented in the article in question¹ involve several methodological flaws that do not allow for decision makers to determine the most adequate resource distribution option. In addition, the cost-effectiveness analysis versus bevacizumab is characterized by lack of transparency in the acquisition of data instead of being based on available scientific evidence.

With regard to the analysis versus cetuximab, an emphasis is made on the difference between the populations in the reviewed article (RAS-WT first line) and in the clinical analysis used to justify the study (KRAS-WT third line). Therefore, in addition to displaying serious methodological doubts, the cost-minimization exercise does not allow for decision making on allocation of resources for patients with mCRC on first line to be supported.

To design a serious analysis that supports decision making on resource distribution, a new model adhering to the CSG methodology would be recommended, since that is the context the study refers, as well as increasing the transparency of the sources of information. In addition, redrawing the methodology is recommended in order to present conservative results towards the treatment of interest and to promote the validity and objectivity of the study.

DECLARATION OF INTEREST

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