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ORIGINAL ARTICLE

Cost-effectiveness of biological therapy compared with methotrexate in the treatment for rheumatoid arthritis in Colombia

Carolina Valle-Mercado · Maria-Fernanda Cubides · Monica Parra-Torrado · Diego Rosselli

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Abstract The objectives of the study are to develop a cost-effectiveness model comparing biological therapy (BT) with methotrexate (MTX) alone, in the treatment for rheumatoid arthritis (RA), combining clinical and quality-of-life data from international trials with local costs and local epidemiological data. We designed a six-month cycle Markov model with five functional states, based on Health Assessment Questionnaire, with patients initiating treatment in any of the predefined states, based on a sample of 150 local RA patients. Simulations ran for 10 and 20 years, and for the whole life span. Utilities, in quality-adjusted life years (QALY), were taken from international literature. Discount rate was 3 % for costs and utilities. We calculated direct and indirect costs using a combination of international and local data. Results are presented as incremental cost-effectiveness ratios (ICER). ICERs in euros per QALY were €143,072 for 10 years; €139,332 for 20 years; and €137,712 for the whole life span. Total costs with MTX were lower than with BT, despite higher out of pocket, productivity, and complication costs. Under conventional thresholds, and for the "average" RA patient, BT would not be cost-effective in Colombia. BT compared to MTX provides more QALYs, but at a high cost. When ICERs were estimated for Colombia, BT would not be cost-effective. We propose different thresholds for different conditions, perhaps prioritizing chronic diseases that lead to disability.

Keywords Rheumatoid arthritis · Cost-effectiveness analysis · Biological therapy · QALY · Colombia

C. Valle-Mercado
Faculty of Economics, Universidad de los Andes, Bogotá, Colombia
e-mail: carovam87@gmail.com

M.-F. Cubides
Rheumatology and Clinical Immunology, Hospital Militar, Universidad de La Sabana, Bogotá, Colombia
e-mail: mfcubides@hotmail.com

M. Parra-Torrado
Fedesarrollo, Bogotá, Colombia
e-mail: mparra@fedesarrollo.org.co

D. Rosselli (✉)
Clinical Epidemiology and Biostatistics Department, Medical School, Pontificia Universidad Javeriana, Carrera 7 No. 40-62, Bogotá, DC, Colombia
e-mail: diego.rosselli@gmail.com

Introduction

Biological therapy (BT) has changed the natural history of rheumatoid arthritis (RA) and has impacted the budget assigned to its treatment [1, 2]. The economic question that arises is if the greater efficacy justifies its higher costs [3–5].

Rheumatoid arthritis, and specifically BT, has been the subject of numerous economic analysis, most of them in developed countries [6, 7]. It has been widely accepted that economic evaluations are not easily generalizable [8]. The case is even more evident when results from developed countries are applied in developing countries where indirect costs, represented in reduced productivity, or earnings lost by disability are much lower due to reduced income.

This paper presents an economic evaluation of BT compared with methotrexate (MTX), from a societal perspective, considering both direct and indirect costs, in a lower middle-income country.

Materials and methods

The model

Using *TreeAge Pro Healthcare 2009* software, we used a cost-utility Markov model (Fig. 1), with 6-month Markov cycles, comparing two treatments for RA: MTX and BT (with or without MTX). We used both a third-party payer (including only direct medical costs) and a societal perspective (including family costs and productivity costs). Discount rate was 3 % both for costs and utilities [9], but was modified in the sensitivity analysis. The program ran for three different horizons: 10, 20 years, and the whole life span of the patient.

Disease states

In each of the two branches of the decision model, the patient could be in any of six states: five determined by the HAQ, and the last one defined as *dead*. The HAQ classifies functional disability ranging from 0 (minimum disability) to 3. The correspondence of disease states and HAQ scores we used is shown in Table 1.

Transition probabilities

An ordered probit was used to estimate the transition probabilities between Markov states, based on the same regression model used by Kobelt et al. [10]. These transition probabilities were obtained by two methods: (1) from a sample of 150 patients followed for 6 months, and (2) from an expert panel (six rheumatologists of the Hospital Militar, a large university hospital in Bogota), using Delphi method, and after a careful appraisal of the literature. In the base case scenario, we used the average of these two calculations, but both were used separately in the sensitivity analysis.

Table 1 Correspondence of HAQ scores and disease states used in the model (based on [11])

State	HAQ score
1	<0.6
2	0.6–<1.1
3	1.1–<1.6
4	1.6–<2.1
5	>2.1
Dead	–

The ordered probit used in the patient sample was estimated with the following formula:

$$\gamma_t = \beta_0 + \beta_1 \times \text{initial}_{\text{age}} + \beta_2 \times \text{gender} + \beta_3 \times \text{onset} + \gamma_{t-1,2} \times s_2 + \gamma_{t-1,3} \times s_3 + \gamma_{t-1,4} \times s_4 + \gamma_{t-1,5} \times s_5 + \varepsilon$$

where γ_t represents the actual HAQ state of the patient, β_0 is a constant, $\text{initial}_{\text{age}}$ is the age of onset of disease, gender is a dummy equal to 1 if the patient is male and 0 if female, onset is time since the onset of disease, and $\gamma_{t-1,1}-\gamma_{t-1,5}$ are dummies that indicate the preceding HAQ state (determined, in this case, with a six-month difference). This regression estimates the annual transition probabilities of our sample. A transition probability is the probability that a patient will be in one state, given that he or she is currently at another state. The explanatory variables include age, gender, and time since the onset of disease.

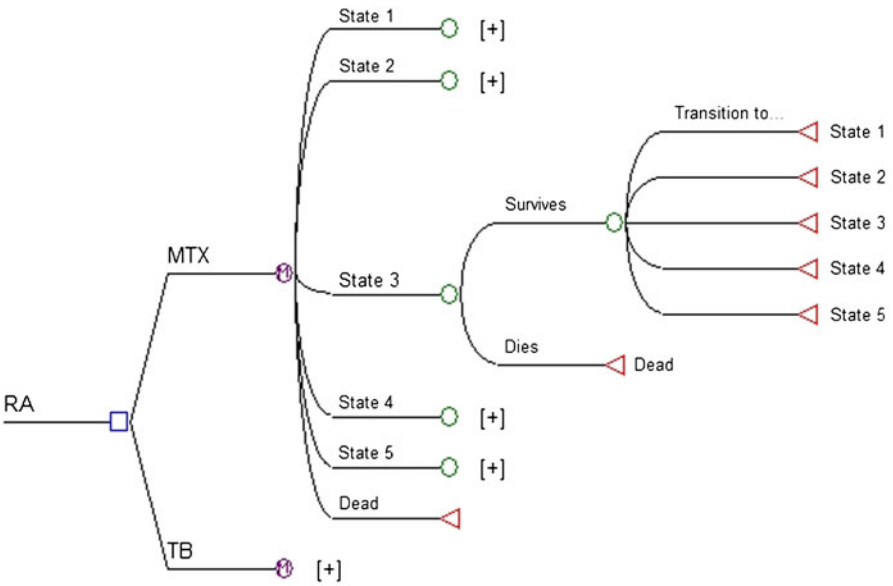

Fig. 1 Structure of the Markov model (adapted from [10]). Patients start the simulation in one of the two branches: methotrexate (MTX) or biological therapy (BT); they also start at an initial state defined by their Health Assessment Questionnaire (HAQ) score (State 1 being the least disability and State 5 the worst). It is assumed that the patients' state depends on their level of inflammation and not on disease sequela. After each 1-year cycle, the patients could be redistributed to different states, depending on improvement, worsening, or death

Patient sample

The convenience sample consisted of 150 patients in different disease stages (male $n = 111$ [74 %]; mean age 58 years); 52 of the (35 %) were receiving BT. The sample was collected between August and October 2009 at the Hospital Militar, one of the largest university hospitals in Colombia. All patients were then followed for 6 months, without modifying their therapy (at least for the purposes of this study). This information was used to estimate both transition probabilities, out of pocket and direct medical costs (with a weighted average for all BT therapies), as well as the proportion of patients in each disease state at the beginning of the study. Apart from collecting information, no intervention was done to the patients. The project was approved by the Ethics Committee of the Hospital.

Mortality

We used standardized mortality ratio (SMR) for the transition probabilities to the state *dead*, applied to Colombian mortality data. The SMR for AR ranges between 1.13 and 3 [12]; we assumed 1.6 as compared with a control person of the same age.

Effectiveness measure (utilities)

The QALYs associated with each Markov state were taken from Kobelt et al. [13] (Table 2), who calculated them using the Euro-Qol based on five dimensions of the disease: anxiety/depression, daily activities, pain/discomfort, self-care, and mobility [14]. Due to the lack of QALY calculations in Colombia, we assumed similar utilities to European studies.

Costs

Costs were classified as direct medical costs, out of pocket, and productivity costs, and were estimated independently for each state. Costs are expressed in euros (1€ ≈3,000 Colombian pesos as of 2009 [15]). Direct medical costs included were health care expenditures such as medication costs, hospitalization, laboratory tests, medical images, medical visits, procedures, complications, and adverse events. The cost of BT was a weighted mean of the patients in the Hospital Militar who received adalimumab, etanercept, infliximab, rituximab, or abatacept. This monthly cost represented €1,101 for BT, as compared to €3 for MTX alone. Out-of-pocket costs included external caregiver (if needed), domestic adaptations, wheelchair, etc.), while productivity costs included job loss, absenteeism, diminished productivity (or presenteeism), which were calculated with the following formula:

$$\text{Indirect cost in state } i = (270 - A_i) * a_i * (OR * b_i) * \bar{w}; \quad \forall i = (1, 5)$$

where A_i is the number of working days missed per year, a_i is a parameter for the relative loss in productivity associated with RA, $\bar{w}$ is the *per diem* salary in Colombia, OR is the occupation rate, and b_i is a parameter that measures the unemployment attributable to RA. Parameter b_i was taken from a French study of 1,487 patients with RA [16] but considered acceptable by our expert panel and the patients in our sample.

Table 3 shows the annual direct health care costs used as inputs in the model for each disease state in euros based on our sample patients. A one-way sensitivity analysis was performed for discount rates, transition probabilities, and for costs of TB.

Results

Table 4 shows the results of both costs and QALYs in the ten-year base case scenario, in the 20-year scenario, and for the whole life span. The ICER decreases as the time horizon increases, as would be expected.

In Table 5, we show the percentage of time that patients spend in each disease state, depending on the treatment selected, with more time spent in less severe disease states in patients treated with biological therapy.

In the sensitivity analysis, using different discount rates, there were no significant changes in the ICER (in the ten-

Table 2 QALYs associated with each Markov disease state

State	QALY
1	0.77
2	0.65
3	0.54
4	0.49
5	0.24

Table 3 Annual direct health care costs used in the model for each disease state, in euros, estimated from a sample of 150 patients from the Hospital Militar, Bogota

State	Medical visits	Laboratory tests and medical images	Hospitalizations
1	104 €	77 €	4 €
2	143 €	95 €	4 €
3	176 €	169 €	5 €
4	241 €	190 €	99 €
5	267 €	220 €	15 €

Table 4 Costs in € and QALYs gained in a ten-year period; annual discount rate 3 % for costs and QALYs

	10 years		20 years		Whole life span	
	MTX	BT	MTX	BT	MTX	BT
Direct medical costs	€25,271	€119,699	€42,330	€199,941	€59,321	€279,864
Out-of-pocket expenses	€3,765	€600	€6,241	€875	€8,692	€1,147
Productivity costs	€1,193	€666	€1,995	€1,092	€2,795	€1,516
Total costs	€30,229	€120,965	€50,566	€201,908	€70,808	€282,527
Incremental costs	–	€90,736	–	€151,342	–	€211,719
QALY	5.41	6.05	9.04	10.13	12.66	14.20
Incremental QALY	–	0.63	–	1.09	–	1.54
ICER	–	€143,072	–	€139,332	–	€137,712

Table 5 Percentage of total time spent in each state, for the 10- and 20-year scenarios for the methotrexate (MTX) and biological therapy (BT)

	10 years		20 years	
	MTX (%)	BT (%)	MTX (%)	BT (%)
State 1	38.1	67.0	36.2	64.8
State 2	33.4	25.9	31.5	24.2
State 3	11.9	2.2	11.4	1.8
State 4	9.1	0.5	8.7	0.3
State 5	3.2	0.1	3.1	0.1

year scenario, ICERs were €141,806, €143,072, and €143,976 per QALY gained with 0, 3, and 5 % discount rates, respectively).

In a second sensitivity analysis, we modified transition probabilities, using either the ordered probit results or the expert consensus, for the 10-year base case scenario. The ICER for the ordered probit increased to €199,711 per QALY gained, while if we use the rheumatologist's estimate, the ICER falls to €61,715 per QALY gained.

Another scenario we considered was with a 20 and a 50 % reduction in the cost of BT starting 3 years from the beginning of the study. In this scenario, ICERs reach a minimum value of €115,555 per QALY gained for the 20 % and €74,281 for the 50 % price reduction, both in the ten-year scenario. Even if we assume both conditions (transition probabilities of the experts combined with the 50 % price reduction in 3 years), the ICERs would still be high (€27,235 per QALY gained) as compared with the per capita GDP per QALY gained.

Discussion

This study has several limitations, common to many modelling exercises in pharmacoeconomics in less developed countries; the lack of local data on the follow-up of patients leads to relying on a combination of foreign literature and expert opinion. To overcome these limitations, we made an effort both to collect primary clinical information from a local university hospital and to estimate direct and indirect costs. The use of an adapted foreign Markov model and the use of QALYs calculated for another population are further limitations of our study.

To our knowledge, there are few economic evaluations applied to RA in Latin America [17], most are limited to estimating the cost of the disease [18–20].

As could be expected, clinical differences between BT and MTX are significant, with BT providing more QALYs to the patients both in all scenarios, and more time in less severe stages of the disease.

This study in Colombia, a lower middle-income country, contrasts with similar studies in developed countries [20]; the main difference strides in our lower out of pocket and productivity costs (grouped in this paper as indirect costs), as seen in Table 4. This can be explained by a much lower average income, which ends up leading to lower productivity losses in people with disabilities. Additionally, most of the patients of our sample were in initial stages of the disease, where disability is less significant. These factors contribute to our conclusion: treatments that prove to be cost-effective in developed countries are not necessarily cost-effective in lower-income countries, where medication costs might be similar, but indirect costs and willingness to pay are both lower. Under every scenario considered, BT, compared with MTX, would not be cost-effective if common thresholds are used (for example, 3 times per capita GDP per QALY, which in the case of Colombia would be up to €10,000 per QALY).

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