Benznidazole for Chagas disease is cost-saving in a European health care setting.

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Abstract

Introduction

Chagas disease is a neglected tropical disease. It is mainly distributed in South America, and it is estimated that 6-7 million people are infected worldwide.[1] Migrations have recently changed the epidemiological picture and made Chagas disease an important issue outside Latin America. USA and Spain are the countries with most migrants from Chagas disease endemic areas and thus the countries with most cases. In Spain it is estimated that 55367 patients live with Chagas disease and 82.5% go untreated.[2] *Trypanosoma cruzi* is mainly transmitted by the hematophagous insect *Triatoma infestans*. When it feeds on humans, it produces a small wound, where it may deposit feces with eggs of *Trypanosoma cruzi*. The parasite may also be acquired by the ingestion of foods contaminated with triatomine feces, by blood transfusion, through pregnancy and delivery as well as through organ transplantation. Most acute infections are asymptomatic and thus may not be identified. In the classical vector-borne infection, symptoms develop after one to two weeks, mainly consisting of fevers, malaise, lymphadenopathy and hepatosplenomegaly. There are characteristic cutaneous signs that may develop, consisting in erythema and swelling at the site of the parasite entrance. This is known as a Chagoma. When the Chagoma develops in the periorbitary structures it is called Romaña´s sign. Acute infection may be severe and have high mortality in patients developing fulminant myocarditis or meningoencephalitis. Patients treated with antiparasitic drugs in the acute phase cure the disease un up to 85% of cases.[3] Patients that are not treated develop the lifelong chronic disease, that may be indeterminate, cardiac, digestive or mixed cardiac and digestive. This chronic infection may be asymptomatic or indeterminate or develop, through a long interplay of diverse cytokines, a heart disease, a digestive disease or a mixed disease.[4] Approximately 30-40% of patients progress from the indeterminate form to the cardiac and/or gastrointestinal disease.

Benznidazole is a 2- nitroimidazole, that is at present the main treatment for *Trypanosoma cruzi* infection. It is indicated in the acute infection, congenital infection, reactivation cases of immunosuppressed patients, women of childbearing age with chronic infection and children with chronic infection.[5] In patients with Chronic determinate or indeterminate Chagas disease and mild disease, it is unclear whether disease progression is haltered by treatment or not.[6] The only clinical trial undertaken so far to evaluate the effect of Benznidazole in patients with chronic Chagas cardiomyopathy, the BENEFIT trial, showed a significant reduction in serum parasite detection, but did not reduce clinical cardiac deterioration through 5 years of follow-up.[7] Moreover, usefulness is limited by

significant toxicity, with poor tolerability profile.[8] Also, at present, Benznidazole is not commercialized in the European Union and not financed in the National Health System in Spain. On the other hand, costs of follow-up of untreated Chagas disease patients and treatment of possible complications in patients that progress to a determinate form is substantial.[9] Therefore, significant doubts arise whether benznidazole treatment may or may not be cost-effective in patients without organ involvement or very mild organ affectation. To address this question this cost-effectiveness evaluation was undertaken.

Methods

Target population and subgroups

Participants were migrants to Spain from South American countries, with ages between 15-69, that had chronic chagas disease, but without organ manifestation or only very mild organ disease. Participants were stratified by sex and by 5-year age groups. Background mortality was adjusted by age group using data from the Spanish National Institute of Statistics.[2,10]

Setting and location

The study evaluates the cost-effectiveness of benznidazole in Spain, in patients with chronic asymptomatic Chagas disease and attended at a specialist infectious disease outpatient clinic. Results are later extrapolated to the rest of the European Union using purchase power parity indicators.

Study perspective

The costs of interventions were derived from a national health care provider perspective. This includes costs only for the government and related to the follow-up and treatment of the patients. Patients' costs, like time and travel costs as well as opportunity costs were not considered.

Comparators

We decided to compare two possible intervention strategies. The base case scenario, a follow-up strategy, where patients with chronic asymptomatic Chagas disease are only followed up and treated for the damage that the parasite may produce (e.g. treatment of

heart failure should it develop). The second scenario is a scenario where every patient with Chagas disease is treated with benznidazole 5-7.5mg/kg/day bid for 60 days.

Outcomes, time horizon and discount rate

Health outcomes were evaluated using Quality-adjusted life-years (QALYs). QALY weights used were taken from Requena-Mendez et al.[11] Each health state had a QALY weight attached to it and total QALYs were calculated for the time horizon. As chronic Chagas disease is a life-time infection, a long-time horizon of 20 years was chosen, and a yearly time-step was considered appropriate. Qalys were discounted at an annual rate of 3% as commonly accepted.[12]

Measurement of effectiveness

As a measure of effectiveness we used the risk reduction of cardiac disease progression reported in the meta-analysis by Crespillo-Andújar et al.[6] We also used the estimate of risk reduction of progression to the intestinal form published by Nunes Da Costa et al.[13]

Costs

Costs used were taken from published insurance reimbursements lists from the Spanish national health system. Cost of Benznidazole was obtained by direct query to the Department for Foreign or Compassionate Use Medicines (Spanish Agency of Medicines). A cost was calculated for each health state of the model considering routine follow-up visits, tests, interventions and frequency of complications in each state (detailed explanation in supplement). Costs were also discounted at an annual rate of 3%.

Model

A Markov model was chosen as Chagas disease is chronic, and patients present several disease states over time.

The model represents a cohort of migrants from south America to Spain with chronic asymptomatic Chagas Disease (figure 1). The model starts with a Chagas disease patient in the upper left corner (Chronic Asymptomatic Chagas Disease), from here a patient may develop Chronic Chagas symptomatic heart disease (upper right corner) or chronic symptomatic Digestive disease (bottom left corner). From All the three mentioned states a patient may die and transition to the fourth state, Death (bottom right corner). The model was stratified by age group and sex. Transitions between states were governed by

parameters presented in table 1. The initial parameters were chosen by extensive literature research by the study investigators and chosen on a qualitative basis.

To calibrate the transition parameters, the model was run 100,000 times and the set or parameters that best reproduced the same deaths due to Chagas disease as those reported by Ramos-Rincón et al.[14] were chosen for the deterministic analysis.

The total population was assumed to remain constant, so deaths were inserted as new patients in the youngest age group.

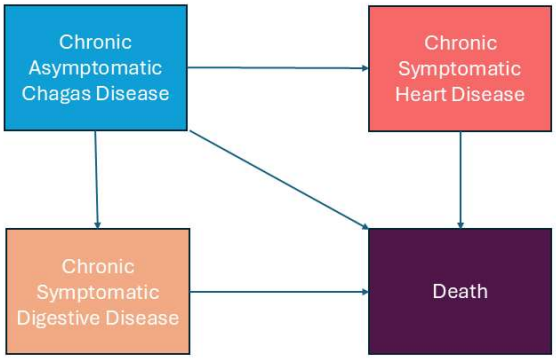

Figure 1. Simplified representation of the Markov model. The model starts with a Chagas disease patient in the upper left corner (Chronic Asymptomatic Chagas Disease), from here a patient may develop Chronic Chagas symptomatic Heart Disease (Right upper corner) or chronic symptomatic Digestive disease (bottom left corner). From All the three mentioned states a patient may die and transition to the fourth state, Death (bottom right corner). The model was stratified by age group and sex.

Data analysis

The model and the analysis was developed in R.[15] The cost effectiveness analysis was undertaken simulating two cohorts, one treated and one not treated with Benznidazol. For each arm, QALYs and costs were calculated with the model as well as the incremental cost-effectiveness ratio (difference in costs divided by difference in QALYs).

A deterministic sensitivity analysis varying key parameters individually among the extreme values within the possible range of values was undertaken and presented as tornado plots. Also, a probabilistic sensitivity analysis (PSA), where the parameters were given probability distributions and the simulations run 1000 times (i.e. Markov Chain Monte-Carlo Simulations) was also undertaken and presented as a scatter plot and cost-effectiveness probability curves. The number of iterations to produce stable results was

estimated by visual inspection of a graphic representation of the cumulative average net monetary benefits (Supplementary material).

As a final calculation the expected value of perfect information was also evaluated.

Reporting of the study was done in accordance with the CHEERS statement.[16]

Results

Study parameters

Transition probabilities derived from literature as well as those obtained after calibration and the distribution used for PSA analysis are presented in table 1.

PARAMETER	MEAN (95% CI)	AFTER CALIBRATION	PSA DISTRIBTUTION	REFERENCE
PROBABILITY OF PROGRESSION TO CARDIAC DISEASE	0.019 (1.3-3.0)	0.0189	Beta (mean=0.0189, 95%CI 0.01-0.03)	Chadalawada et al. 2020[17]
RELATIVE RISK MORTALITY DUE TO CHAGAS CARDIAC DISEASE	12 (4-16)	2.57	LogNormal (mean=2.57, 95% CI 1.1-5)	Chadalawada et al. 2021[18]
RELATIVE RISK MORTALITY DUE TO CHAGAS DIGESTIVE DISEASE	2.1 (1.52-2.91)	1.25	LogNormal (mean=1.25, 95% CI 1-2)	by Cucunuba et al. 2016.
PROBABILITY OF TRANSITIONING INTO STATE WITH CHAGAS DIGESTIVE DISEASE	0.011 (0.008-0.0136)	0.035	LogNormal (mean=0.035, 95% CI 0.01-0.04)	Castro et al. 1994[19]

RELATIVE RISK REDUCTION OF PROGRESSION TO CARDIAC CHAGAS DISEASE	0.49 (0.19-1.25)	NA	LogNormal (mean=0.49, 95% CI 0.019-1.25)	Crespillo-Andújar et al. 2022[6]
RELATIVE RISK REDUCTION OF PROGRESSION TO DIGESTIVE CHAGAS DISEASE	0.88 (0.55-1.42)	NA	LogNormal (mean=0.88, 95% CI 0.55-1.42)	Nunes da costa et al. 2021[13]

Table 1. Model parameters that govern transitions between states.

Costs

Costs used in the model are presented in table 2.

ITEM	UNIT COST (€)	ANNUAL UNITS	ANNUAL COST (€)	SOURCE
TREATMENT	131.00	Once	7.00	Direct query to the Department of foreign medicines of the Spanish Agency of Medicines and Medical Devices.
COMPLETE BLOOD COUNT (CBC)	10.00	2	20.00	BOJA 2024.[20]
BASIC BIOCHEMISTRY	20.00	2	40.00	BOJA 2024.[20]
ECG	40.00	2	80.00	BOJA 2024.[20]

ECHOCARDIOGRAM	100.00	0.05–1	5.00–100.00	BOJA 2024.[20]
***TRYPANOSOMA CRUZI* SEROLOGY**	20.00	2	40.00	BOE 2023.[21]
***TRYPANOSOMA CRUZI* PCR**	44.26	2	88.52	BOE 2023.[21]
CARDIAC PACEMAKER (MCP)	6,000.00	0–0.02	0.00–120.00	BOJA 2024.[20]
HEART TRANSPLANT	100,000.00	0–0.01	0.00–1,000.00	BOJA 2024.[20]
IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD/DAI)	25,000.00	0–0.03	0.00–750.00	BOJA 2024.[20]
BARIUM ENEMA	80.00	0.05–1	4.00–80.00	BOJA 2024.[20]
BARIUM ESOPHAGEAL TRANSIT STUDY	90.00	0.05–1	4.50–90.00	BOJA 2024.[20]
GASTROSCOPY	150.00	0–1	0.00–150.00	BOJA 2024.[20]
ESOPHAGEAL MANOMETRY	1,955.00	0–0.05	0.00–97.75	BOJA 2024.[20]
SURGERY	6,277.00	0–0.01	0.00–62.77	BOJA 2024.[20]
ENDOSCOPIC SPHINCTEROTOMY	978.00	0–0.01	0.00–9.78	BOIB 2021.[22]
MEDICAL CONSULTATION	98.00	2	196.00	BOIB 2021.[22]
SACUBITRIL/VALSARTAN	705.21	12	8,462.52	Spanish retail price.

BISOPROLOL	5.93	12	71.16	Spanish retail price.
DAPAGLIFLOZIN	46.02	12	552.24	Spanish retail price.
FUROSEMIDE	2.25	12	27.00	Spanish retail price.
HOSPITALIZATION	2,727.32	0–0.04	0.00–109.09	Delgado et al.[23]

Table 2. Unit cost and utilization reflect average or typical values used in the cost-effectiveness model of Chagas disease management. Ranges are shown where item use varies by clinical state (asymptomatic, cardiac, digestive).

CEA analysis

In the no treatment arm, the model produced a total of 699,944.2QALYs and cost €1,592,765,694.7. In the Benznidazole arm, a total of 703,251.6 QALYs were obtained (i.e. an increase of 3,307.4 QALYs) at a total cost of €1,032,673,731.6. This represents total savings of €560,091,963, yielding an ICER of €-169,342.3/QALY gained (table 3).

TREATMENT	**QALYS**	**COSTS (2023€)**	**INCREASE IN QALYS**	**INCREASE IN COSTS**	**ICER 2023€/ QALYS GAINED**
NO TREATMENT	699,944.2	1,592,765,694.7	NA	NA	NA
BENZNIDAZOL	703,251.6	1,032,673,731.6	3,307.4	-560,091,963	-169,342.3

Table 3. Costs, Qalys and Incremental Cost-effectiveness ratios of BZN. NA: Not applicable. ICER: Incremental cost effectiveness ratio. QALYs: Quality adjusted life-years.

In the deterministic sensitivity analysis the only parameter that would modify the ICER yielding it not cost-saving was the highest value of the relative risk of developing the symptomatic cardiac form of Chagas disease. Nevertheless, it still fell below the cost-effectiveness threshold of one time the GDP-per capita of Spain (figure 2).

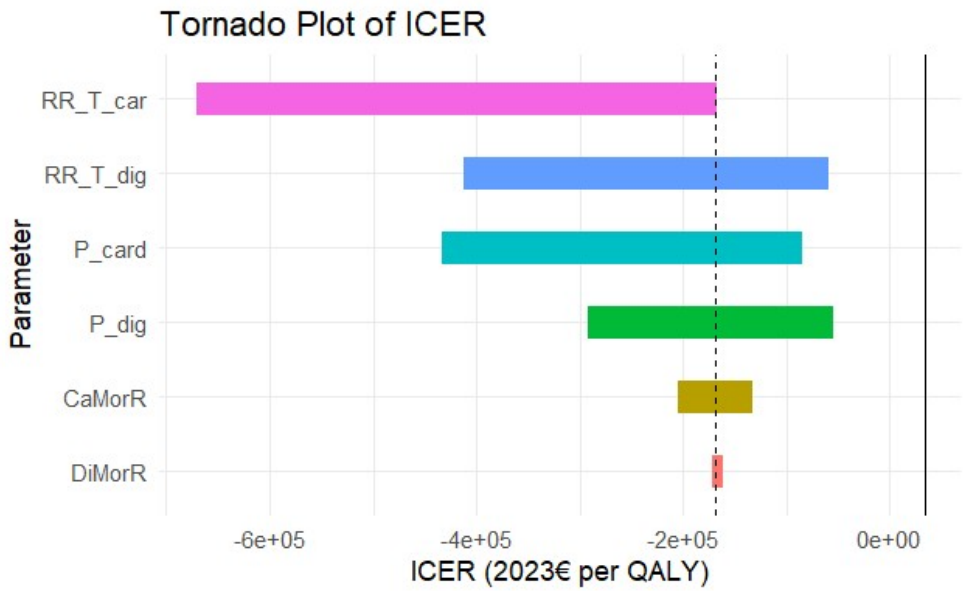

Figure 2. Tornado plot of the incremental cost-effectiveness ratio (ICER) expressed in 2023 Euros per quality-adjusted life year (QALY) gained. The plot displays the results of a one-way sensitivity analysis assessing the impact of individual parameter uncertainty on the ICER. Parameters are ordered by their influence, with the widest bars indicating the greatest effect. P_card: probability of cardiac involvement; P_dig: probability of digestive involvement; RR_T_car and RR_T_dig: relative risk reductions with treatment in cardiac and digestive forms, respectively; CaMorR and DiMorR: increase mortality ratios in cardiac and digestive forms. The vertical dashed line indicates the base-case ICER. The vertical line indicates the willingness to pay threshold.

In the probabilistic sensitivity analysis the median ICER was €-69,372 (95% CrI; €-177,181.16: €-26,488.9), with 95% of the simulations falling below the WTP.

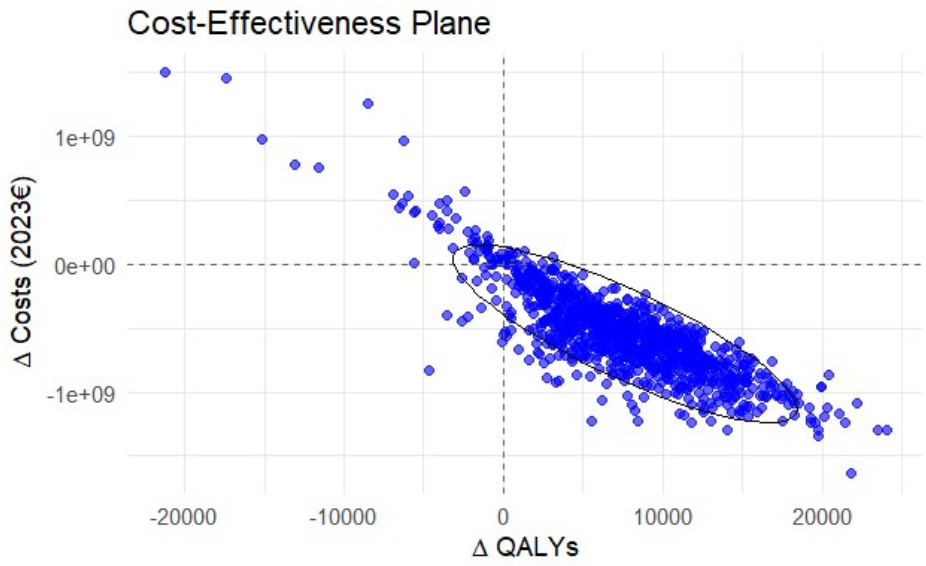

Figure 3. Cost-effectiveness plane based on 1,000 probabilistic simulations. Each point represents the incremental costs and QALYs of the intervention compared to the comparator under one simulation draw. Most simulations fall in the southeast quadrant, indicating that the intervention is both cost-saving and more effective. All costs are expressed in 2023 euros (€).

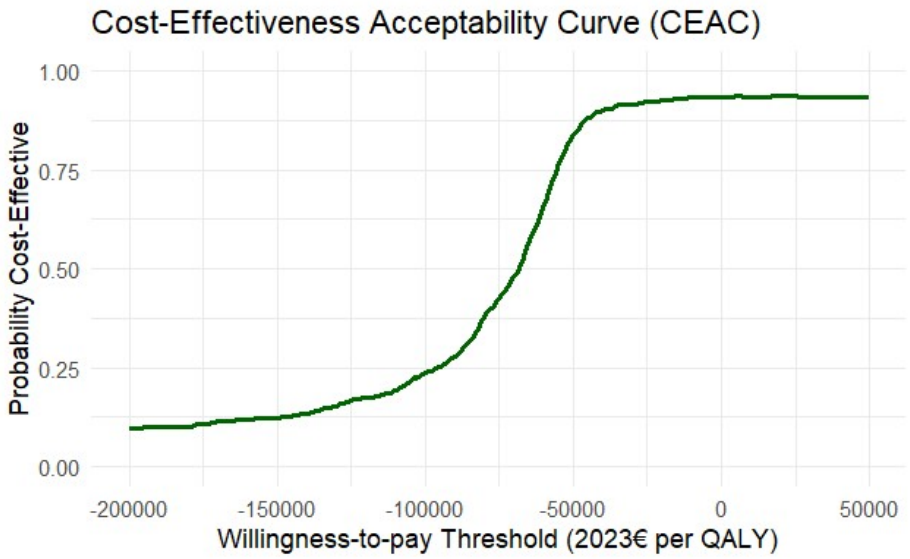

Figure 4. Cost-Effectiveness Acceptability Curve (CEAC) showing the probability that the intervention is cost-effective across a range of willingness-to-pay (WTP) thresholds per QALY gained. The curve illustrates increasing confidence in cost-effectiveness as the WTP threshold rises, with near-certainty achieved above approximately –€25,000 per QALY.

The expected value of perfect information (EVPI) was €24,946,099 meaning €1,247,305 per year or €22.78 per patient and year.

Discussion

In our study, we found benznidazole to be a cost-saving treatment for the treatment of patients with asymptomatic Chagas disease, as the study arm treated with benznidazole not only yielded more QALYs but also ended up with less total costs. Moreover, both the deterministic sensitivity analysis and the PSA show us the same results, pointing out that the results are robust. Only the most extreme values of the effectiveness of benznidazole in reducing the progression to cardiac disease increased the ICER and made it not cost-effective, however it still fell below the WTP.

At present, benznidazole is not covered free of cost in the Spanish health system. However, in the light of these results it would seem reasonable, especially when coupled with the fact that previous studies have found Chagas disease screening programs to be cost-effective .[11,24] On top of this, we have not accounted for the QALYs gained from avoiding congenital transmission of disease. Such cases are estimated to be happening in Spain.[25]

In the Deterministic sensitivity analyses, we did not find any variable that would render benznidazole not cost-saving. In the probabilistic sensitivity analysis the most likely result would be that Benznidazole is cost-savin with more than 95% of the simulations falling well below the WTP. Nevertheless, some uncertainty remains and thus the EVPI was calculated and established at €1.2 million per year over the study period. Meaning that this should be the amount a health policy maker would be willing to pay for the uncertainty reduction derived from the perfect information. This data has important implications when allocating funds for research.

The strengths of our study are that we calibrated the model to reflect the Spanish epidemiological situation, allowing to better evaluate the need. Also, comprehensive sensitivity analyses were undertaken and despite modifying the variables to extreme values the results point in the same direction, benznidazole is cost-saving. We also have determined the EVPI to help guide funding decisions of scientific studies that would improve the model and reduce the uncertainty.

The weaknesses of the study are to be acknowledged. First, we assume a constant population of migrants, which may be somewhat unrealistic. Also, there are several study parameters that have a great deal of uncertainty. However, this has been accounted for in extensive sensitivity analyses and the EVPI reported.

Our study suggests that benznidazole is a cost-saving drug for the treatment of patients with chronic asymptomatic Chagas disease. Health policy makers should be willing to fund up to €1.2 million per year to achieve perfect information for decision making.

Use of AI:
AI tools (specifically OpenAI's ChatGPT) were used throughout the study to assist in code development, the formatting of manuscript text and tables, and to improve the overall clarity and readability of the writing. All outputs generated by AI were reviewed and verified by the authors for accuracy, scientific validity, and appropriateness. No content was generated without human oversight, and the final responsibility for all aspects of the manuscript lies with the authors.

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