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Cost-effectiveness of velmanase alfa *vs.* bone marrow transplantation or no causal therapy in patients with mild to moderate alpha-mannosidosis

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ABSTRACT

Alpha-mannosidosis is an inherited rare disorder of mannose-containing oligosaccharides metabolism that is currently treated by enzyme replacement therapy (ERT), bone marrow transplantation (BMT), or supportive therapy (ST). However, the relative cost-effectiveness of these treatment options is yet unknown. Our study aimed to compare the cost-effectiveness of the treatment options for mild to moderate alpha-mannosidosis. The study is based on a modeling approach using a Discrete-Event Simulation model to generate and simulate the course of the disease under the influence of each of the treatment options: ERT, BMT, and ST. The model had a lifetime horizon and was made from the perspective of the Serbian Health Insurance Fund. Currently, available causal therapy of mild to moderate alpha-mannosidosis with velmanase alpha enzyme replacement is not cost-effective compared with supportive therapy (ICER = 941,587,152 RSD) or bone marrow transplantation (ICER = −398,412,755 RSD). Bone marrow transplantation can be cost-effective compared to supportive therapy (ICER = 6,032,689 RSD), but only if the willingness-to-pay threshold is increased to 9 gross domestic products (GDP) per capita per QALY gained. According to the current threshold, velmanase-alfa is not cost-effective compared to BMT or ST. To make alfa-mannosidosis therapy widely accessible to patients, criteria for assessing the cost-effectiveness of orphan drugs must include not only the absolute value of ICER but other aspects like equity weightings of QALYs, risk-sharing, reimbursement of severe forms of a disease only, or availability of dedicated funding.

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KEYWORDS
Velmanase alfa; alpha-mannosidosis; cost-effectiveness; bone marrow transplantation; discrete event simulation

Introduction

Alpha-mannosidosis is a disorder of mannose-containing oligosaccharides metabolism. The condition is autosomal recessive (the gene with function-losing mutations is designated as *MAN2B1* located on chromosome 19) [1]. It is caused by decreased activity of lysosomal alpha-mannosidase, which leads to the accumulation of mannose-containing oligosaccharides in tissues [2,3]. The frequency of alpha-mannosidosis is about 1:500,000 live births. Three clinical forms of alpha-mannosidosis have been described: type 1—the mild form that starts after ten years of age (slowly progressive, without skeletal abnormalities); type 2—the moderate form (slowly progressive, with skeletal abnormalities); and type 3—severe infantile form [3]. However, this classification is only conditional regarding the differentiation between mild and moderate forms since many patients have mixed clinical characteristics. The main clinical features of the disease are ataxia due to cerebellar atrophy, myopathy, arthrosis, delay of mental development and overall mental impairment in later age, skeletal abnormalities resulting in a coarse face, kyphosis or scoliosis, hearing impairment, hepatosplenomegaly, frequent otitis media, and pneumonia occurrence, and behavioral problems/psychosis [1].

If not treated, even mild to moderate alpha-mannosidosis has a progressive course, with hearing impairment at 3rd year of life, notable mental impairment at 6th year, abnormal behavior/psychosis at the 26th year of life, and death at about the age of 40. Currently, two treatment modalities may delay

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the progression of this rare disease: bone marrow transplantation (BMT) and enzyme replacement therapy (ERT) [4]. However, experience from clinical trials and case series is insufficient to estimate the effectiveness of both therapeutic options (concerning hard outcomes, mental impairment, and mortality) as well as the total treatment costs, including adverse effects. In a phase III clinical trial, enzyme replacement therapy with velmanase alpha resulted after a year of treatment with a 77.6% reduction in serum oligosaccharides and −1.1% change in a 3-min stair-climb test [5]. In an extension study, the patients received velmanase alpha for 29.3 months; serum oligosaccharide levels were reduced by 62.8%, and the mean improvement of the 3-min stair-climb test at the last observation was 13.8% [6]. A recent study on long-term velmanase alfa treatment in young children showed improvements in various efficacy assessments, suggesting the treatment is acceptably safe, well-tolerated, and may provide benefits to patients under 6 years of age [7].

For innovative ERT of alpha-mannosidosis to be used, it is necessary to prove a favorable cost-effectiveness ratio (in comparison with placebo and with the best standard of care therapy), i.e. that the costs per quality-adjusted life years are acceptable for health insurance funds, which should cover the cost of therapy for specific patients. The cost-effectiveness of causal alpha-mannosidosis therapy remains open; even in the most developed countries of the world, the cost-effectiveness of velmanase alpha has not yet been confirmed [8]. Causal therapy of rare diseases is a great burden for any health insurance fund [9,10], so it is important to determine precisely how much is invested in the health of the population with alpha-mannosidosis and whether it is possible to bear such costs given the available budgets.

A cost-effectiveness study of velmanase alfa compared to BMT and supportive therapy (no causal therapy) from the perspective of the Health Insurance Fund of the Republic of Serbia or other countries has not yet been reported in medical journals. Our study aimed to compare the costs and effectiveness of velmanase alfa with the costs and effectiveness of BMT treatment and supportive therapy (no causal therapy) of mild to moderate alpha-mannosidosis. In addition, we also compared BMT with supportive therapy (no causal therapy).

Methodology

A pre-established study plan for this health economic analysis was created and the study was carried out following this protocol. The study plan is available at: https://osf.io/gs756/.

The study involved utilizing a Discrete-Event Simulation (DES) model [11–13] to generate and simulate the course of alpha-mannosidosis, where the conditions (states) of the disease were only changed at discrete points in time. The model population was composed of patients affected by mild to moderate alpha-mannosidosis, and their attributes in the model were: the age at the onset of the disease, signs and symptoms of disease deterioration, and treatment administered with expected beneficial and adverse effects. Events defined in the model were patients' health states changes, initiating activities that were associated with costs and quality of life changes with the events and the updated states: hearing impairment, mental impairment, cerebellar atrophy and cerebellar demyelination (columnar disease)—fall, abnormal behavior, skeletal and muscular abnormalities—fall, vision loss, hernia, hepatosplenomegaly, coarse face, otitis media—three episodes, pneumonia—two episodes, and death. The simulated time was divided into equal increments of one month, and fixed-increment time advance was used as a mechanism of the simulated time advancement with a lifetime horizon of 60 years. The model was designed from the perspective of the Serbian Health Insurance Fund; Republic of Serbia is classified by the World Bank as an upper-middle-income country. Figure 1 shows the model and its assigned attributes and events.

Treatment strategies taken as comparators in our model were velmanase alfa, bone marrow transplantation (BMT), and no causal therapy (supportive disease therapy). We created three scenarios depending on comparators, and a model simulation was conducted for each. Scenario simulations were analyzed separately for Scenario 1: velmanase alfa *vs.* no causal therapy, Scenario 2: velmanase alfa *vs.* BMT, and Scenario 3: BMT *vs.* no causal therapy. Model inputs, variability, PSA values, and references to support the model inputs for events are provided in Table 1. Quality-of-life decrements and costs, per episode and sustained, are provided in Table 2. For other researchers to be able to use the costs obtained in our analysis, we expressed them additionally as a % of the Serbian gross domestic product (GDP) per capita.

In the model, only direct costs were used, and they, along with the effects, were discounted from the second year at a single annual rate of 6.0% [37]. All the costs are expressed in Serbian monetary units—Republic of Serbia Dinar (RSD). The exchange rate used for calculation was, 1 EUR = 117.5836 RSD. Treatment

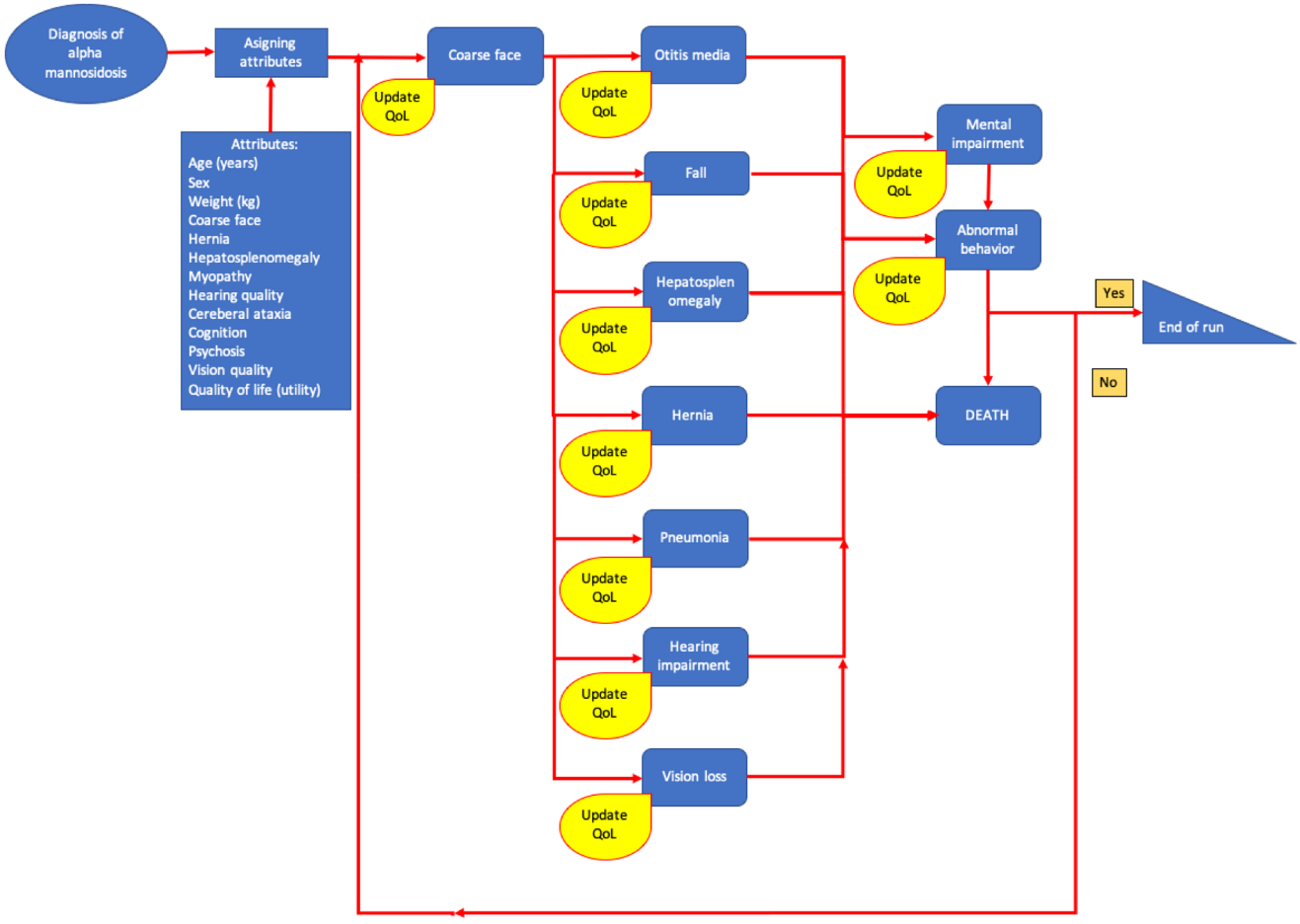

Figure 1. DES model representation. Blue rectangles are events that may happen during the lifetime of a patient, each updating quality of life and costs; some events are short-lasting, so they update costs and effects only during the time increment of one month, and some are long-lasting, updating costs and effects on quality of life until the end of a patient's life. The arrows show the direction of movement of a patient during one model increment. After the pre-defined number of one-month model increments ($n = 720$), the model stops, total costs and effects are calculated for the current patient, and then another virtual patient enters.

total direct costs taken into account were the costs of procuring medicines, the costs of health services provided during the treatment of the underlying disease, the costs of diagnostics, and the costs of treating side effects. These costs were either calculated manually following clinical practice guidelines, unit prices of health services from the Tariff Book of Health Insurance Fund [38], or taken from other published pharmacoeconomic studies. When data on costs were taken from pharmacoeconomic studies from other countries, first, we expressed those costs as the % GDP of the country where the study was conducted and then multiplied it by Serbian GDP.

Since velmanase alfa is an unauthorized drug in Serbia and does not have an officially published price [39,40], we used the local regulation to define the potential maximum price of the drug [40]. For the calculation of maximum wholesale price, the regulation in Serbia takes into account the lowest price in three reference countries (Slovenia, Italy, and Croatia) in case of reference drug, or if the price is not available in these countries, then the price in the country of origin or average of drug prices in the European Union countries is used. Since in the previously mentioned reference countries, there is no price for this drug, the price for one vial of velmanase alfa (10 mg, powder for infusion) used in the model was the average price of this medicine in the European countries (Romania, Lithuania, Slovakia, France, Denmark, and Luxembourg) where prices for this medicine were publicly available (other countries do not have a price for velmanase alfa). Prices for other drugs were the prices from the List of drugs that are prescribed and issued at the expense of the funds of the obligatory health insurance in Serbia [41] or from the Decision on the maximum prices of medicines of the Government of the Republic of Serbia [39]. For the drugs that did not have any officially published price in Serbia, we used the price of that medicine in

Table 1. Model inputs for events onset.

Input parameter	Treatment option	Base case mean value with variability (months)	References
Time to hearing impairment	No causal therapy	30.00 ± 6.00	[14,15]
	Velmanase alfa	61.30 ± 6.00	[6,14–16]
	BMT	96.00 ± 6.00	[14,15,17]
Time to mental impairment	No causal therapy	60.00 ± 12.00	[14,15]
	Velmanase alfa	60.00 ± 12.00	[14,15]
	BMT	126.00 ± 12.00	[14,15,17]
Time to cerebral atrophy and cerebral demyelination (columnar disease)—fall	No causal therapy	120.00 ± 24.00	[14,15]
	Velmanase alfa	120.00 ± 24.00	[14,15]
	BMT	186.00 ± 24.00	[14,15]
Time to abnormal behavior	No causal therapy	180.00 ± 60.00	[14,15]
	Velmanase alfa	180.00 ± 60.00	[14,15]
	BMT	246.00 ± 60.00	[14,15]
Time to skeletal and muscular abnormalities—fall	No causal therapy	170.00 ± 60.00	[14,15]
	Velmanase alfa	201.30 ± 60.00	[6,14–16]
	BMT	236.00 ± 60.00	[14,15,17]
Time to vision loss	No causal therapy	300.00 ± 80.00	[14,15]
	Velmanase alfa	331.30 ± 80.00	[6,14–16]
	BMT	366.00 ± 80.00	[14,15,17]
Time to hernia	No causal therapy	36.00 ± 18.00	[14,15]
	Velmanase alfa	36.00 ± 18.00	[14,15]
	BMT	36.00 ± 18.00	[14,15]
Time to hepatosplenomegalia	No causal therapy	6.00 ± 2.00	[14,15,17]
	Velmanase alfa	6.00 ± 2.00	[14,15]
	BMT	6.00 ± 2.00	[14,15]
Coarse face	No causal therapy	4.00 ± 2.00	[14,15]
	Velmanase alfa	4.00 ± 2.00	[14,15]
	BMT	4.00 ± 2.00	[14,15]
Otitis media—1st episode	No causal therapy	18.00 ± 6.00	[14,15]
	Velmanase alfa	18.00 ± 6.00	[14,15]
	BMT	18.00 ± 6.00	[14,15]
Otitis media—2nd episode	No causal therapy	24.00 ± 4.00	[14,15]
	Velmanase alfa	24.00 ± 4.00	[14,15]
	BMT	24.00 ± 4.00	[14,15]
Otitis media—3rd episode	No causal therapy	38.00 ± 6.00	[14,15]
	Velmanase alfa	38.00 ± 6.00	[14,15]
	BMT	38.00 ± 6.00	[14,15]
Pneumonia—1st episode	No causal therapy	130.00 ± 24.00	[14,15]
	Velmanase alfa	161.30 ± 24.00	[6,14–16]
	BMT	196.00 ± 24.00	[14,15,17]
Pneumonia—2nd episode	No causal therapy	240.00 ± 60.00	[14,15]
	Velmanase alfa	271.30 ± 60.00	[6,14–16]
	BMT	306.00 ± 60.00	[14,15,17]
Death	No causal therapy	480.00 ± 120.00	[14,15]
	Velmanase alfa	511.30 ± 120.00	[6,14–16]
	BMT	546.00 ± 120.00	[14,15,17]

the neighboring countries taking into account the Serbian regulation on drug pricing [40].

The effects of the treatment were expressed as the gained years of life adjusted for quality (QALY). The same approach for comparators (BMT and symptomatic therapy of the disease complication) was used. We calculated QALYs gained and direct costs for our comparators, and we expressed the outcome of our study in incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB). ICER was calculated as the difference in comparators' costs divided by the difference in comparators' effects, while NMB was calculated as the difference in QALYs gained multiplied by a willingness to pay.

The DES model was created using Microsoft Excel 2019 and simulated using the Monte Carlo simulation (specially written Macros created by SJ and IS using Virtual Basic) for cohorts of 1000 virtual individuals, and the mean, standard deviation, and confidence intervals at the 99% probability level were calculated for each of the output parameters (effects of therapeutic options, costs of therapeutic options, the difference in effects, the difference in costs, incremental ratio costs and effects and net monetary benefit). One-way and probabilistic sensitivity analyses were conducted to test the model's resilience.

Results

Base case

According to the base case Monte Carlo microsimulation for 1000 virtual patients, the results expressed as average cost per patient (CPP), the average number of

Table 2. Quality-of-life decrements and costs per episode and sustained.

	QoL decrement per episode	Sustained QoL decrement per month	References for QoL	COSTs per episode (RSD)	COSTs per episode (% of GDP)	Sustained COSTs per month (RDS)	Sustained COSTs per month (% of GDP)	References for COSTs
Hearing impairment	0.027	0.027	[18]	82,422.83	8.98	4,422.83	0.48	[19,20]
Mental impairment	0.048	0.048	[21]	6,880.81	0.75	6,880.81	0.75	[22]
Cerebral atrophy and cerebral demyelination (columnar disease)—fall	0.042	0.042	[23]	7,274.03	0.79	0.00	0.00	[24]
Abnormal behavior	0.104	0.104	[25]	14,558.01	1.59	14,558.01	1.59	[26]
Skeletal and muscular abnormalities—fall	0.042	0.042	[23]	7,274.03	0.79	7,274.03	0.79	[24]
Vision loss	0.244	0.244	[27]	15,498.06	1.69	15,498.06	1.69	[28]
Hernia	0.000	0.000	/	70,643.03	7.70	0.00	0.00	[29]
Hepatosplenomegalia	0.060	0.060	[30]	2,828.78	0.31	2,828.78	0.31	[31]
Coarse face	0.000	0.000	/	0.00	0.00	0.00	0.00	/
Otitis media—1st episode	0.210	0.000	[32]	5,504.65	0.60	0.00	0.00	[33]
Otitis media—2nd episode	0.210	0.000	[32]	5,504.65	0.60	0.00	0.00	[33]
Otitis media—3rd episode	0.210	0.000	[32]	5,504.65	0.60	0.00	0.00	[33]
Pneumonia—1st episode	0.150	0.000	[34]	47,268.61	5.15	0.00	0.00	[35]
Pneumonia—2nd episode	0.150	0.000	[34]	47,268.61	5.15	0.00	0.00	[35]
Death	0.000	0.000	/	0.00	0.00	0.00	0.00	/

QoL: quality of life; GDP: Gross Domestic Product per Capita for Serbia in 2021 was 917,441.90 RSD [36].

QALYs, ICER per additional QALY achieved are shown for Velmanase alfa treatment compared to no causal therapy—supportive therapy (Scenario 1), to BMT (Scenario 2), and also treatment with BMT compared to no causal therapy (Scenario 3).

Scenario 1

The average CPP with velmanase alfa was 369,962,433 ± 2,820,549 RSD (99% CI), and the average number of QALYs gained was 12.32 ± 0.06. For patients receiving standard-of-care therapy, the average CPP was 4,363,614 ± 75,111 (99% CI), with the average number of QALYs gained 11.94 ± 0.08. Velmanase alfa's ICER per additional QALY achieved as compared to no causal therapy was 941,587,152 ± 7,265,674 RSD (99% CI), while the net monetary benefit was negative at −365,242,595 ± 2,779,403 RSD (99% CI).

Scenario 2

The average CPP with velmanase alfa was 369,069,137 ± 2.958,665 RSD (99% CI), and the average number of QALYs gained 12.31 ± 0.07. For patients on BMT, the average CPP was 12,391,975 ± 52,455 (99% CI), with the average number of QALYs gained 13.21 ± 0.05. Velmanase alfa's ICER per additional QALY achieved as compared to BMT was −398,412,755 ± 3,305,129 (99% CI), while the net monetary benefit was negative at −357,498,497 ± 2,912,279 RSD (99% CI).

Scenario 3

The average CPP on BMT was 12,350,830 ± 52,201 RSD (99% CI), and the average number of QALYs gained was 13.24 ± 0.05. For patients on no causal therapy, the average CPP was 4,347,896 ± 74,744 (99% CI), with the average number of QALYs gaining 11.91 ± 0.07. BMT's ICER per additional QALY achieved as compared to no therapy was 16.032.689 ± 69.063 (99% CI), while the net monetary benefit was negative at −6,785,860 ± 101,332 RSD (99% CI).

The ICER is displayed separately for each virtual patient for all three scenarios and is shown in Figure 2. In addition, ICER CI (average values of QALYs, costs ± CI 99%) is also shown in Figure 3.

The velmanase alfa therapy was extendedly dominated by a linear combination of BMT and no causal therapy because both BMT and no causal therapy are much less costly than velmanase alfa. BMT is more effective (difference in QALYs gained is 0.9), and no causal therapy is less effective (difference in QALYs gained is 0.4) than velmanase alfa; their combination is still more effective on a population level (0.5 QALYs gained per patient on average).

Acceptability curve

The Health Insurance Fund willingness to pay is shown as Acceptability curves for all three scenarios for the base case and after PSA (Supplementary File A).

One-way sensitivity analysis

One-way sensitivity analysis was conducted for all three scenarios varying the input variable values by 50% for each one, and the net monetary benefit for each of the different values was obtained. Six of the

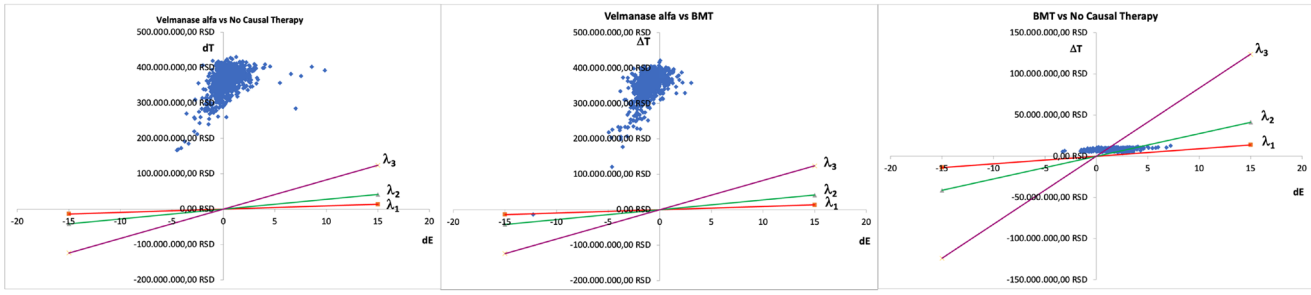

Figure 2. ICER for three scenarios. Incremental cost-effectiveness planes for the three scenarios: velmanase alfa *vs.* no causal therapy, velmanase alfa *vs.* bone marrow transplantation (BMT), and BMT *vs.* no causal therapy. Each dot on the graphs is one virtual patient ($n = 1000$ virtual patients); λ_1, λ_2, and λ_3 are cost-effectiveness thresholds of 1 Gross domestic Product (GDP) per capita per quality adjusted life year (QALY) gained, 3 GDPs per capita per QALY gained and 9 GDPs per capita per QALY gained, respectively. X-axis: difference in effects in QALYs (dE); Y-axis: difference in costs (dT).

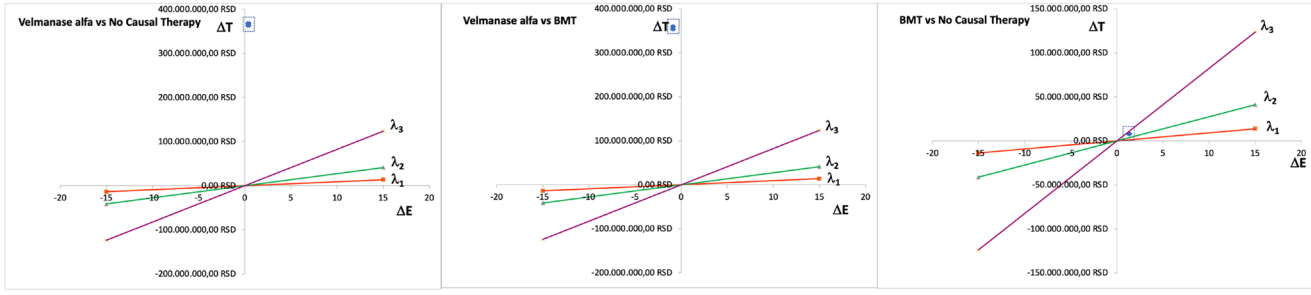

Figure 3. ICER CI for three scenarios. Incremental cost-effectiveness planes for the three scenarios: velmanase alfa *vs.* no causal therapy, velmanase alfa *vs.* bone marrow transplantation (BMT), and BMT *vs.* no causal therapy. Blue dots on the graphs within the blue squares represent incremental cost-effectiveness ratio (ICER) with its 99% confidence intervals (CIs); λ_1, λ_2, and λ_3 are cost-effectiveness thresholds of 1 Gross domestic Product (GDP) per capita per quality adjusted life year (QALY) gained, 3 GDPs per capita per QALY gained and 9 GDPs per capita per QALY gained, respectively. X-axis: difference in effects in QALYs (dE); Y-axis: difference in costs (dT).

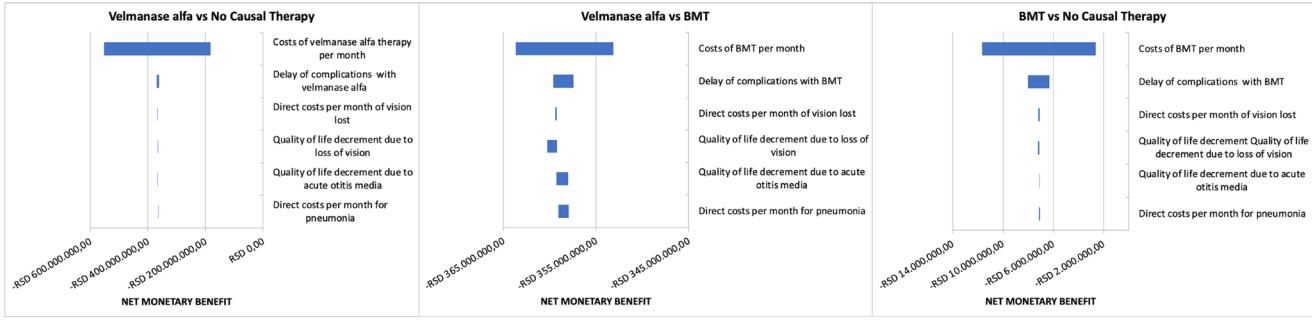

Figure 4. Tornado diagram for three scenarios. One-way sensitivity analysis for the three scenarios: velmanase alfa *vs.* no causal therapy, velmanase alfa *vs.* bone marrow transplantation (BMT), and BMT *vs.* no causal therapy. X-axis: net monetary benefit (NMB) if the first therapeutic option is used instead of the comparator. Blue bars on the graphs represent the variation range of the NMB if input parameters (shown on the right of the respective bars) are decreased and increased by 50%.

most important factors are selected and shown as the study results in the Tornado diagrams (Figure 4).

According to a one-way sensitivity analysis, for Scenarios 1 and 2, the cost of velmanase alfa, vision loss, and delay of complications with BMT have the most effects on net monetary benefit or the cost-utility of velmanase alfa. Velmanase alfa does not become cost-effective even if these variables have extreme values in their favor because the net monetary benefit is still negative. On the other hand, for Scenario 3, the cost of BMT, costs of vision loss, and delay of complications with BMT have the most effects on the net monetary benefit or the cost-utility of BMT. BMT does

not become cost-effective even if these variables have extreme values.

Probabilistic sensitivity analysis (PSA)

In the model, the beta distribution was used to describe the rate and utility variables, while the gamma distribution described the cost variables. Time to events in the model was described using the normal distribution. These distributions were entered into the model as input variables, and the simulation generated PSA output. The output variables had values similar to those in the base case, and their mean values were not too different from the base case (Table 3). Velmanase alfa was not a cost-effective treatment option for alfa-mannosidosis compared to no causal therapy or bone marrow transplantation, as shown by the PSA. Despite the range of input variables, velmanase alfa consistently exceeded the cost-effectiveness threshold for ICER, also resulting in a negative net monetary benefit.

On the other hand, BMT may be considered cost-effective if a threshold is higher than 3 GDP, which some authors consider appropriate in the case of orphan medicines [42].

Discussion

Our study showed that the currently available causal therapy for mild to moderate alpha-mannosidosis with velmanase alpha enzyme replacement therapy is not cost-effective compared with supportive therapy or bone marrow transplantation from the perspective of the Serbian Health Insurance Fund. Bone marrow transplantation can be a cost-effective treatment option compared to supportive therapy, but only if the willingness-to-pay limit of the Health Insurance Fund in Serbia is increased to 9 GDP per capita per one gained year of life adjusted for quality.

This result is not surprising because so far, it has been shown that causal therapy through the substitution of missing or dysfunctional enzymes carries costs per QALY gained that many times exceed the acceptable cost-effectiveness limit for other hereditary and rare diseases in almost all countries of the world [43]. The reason for such an unfavorable cost-effectiveness ratio lies in the very nature of the diseases being treated and in the high costs of developing causal therapy for such conditions. Not only do rare hereditary diseases have a low prevalence, but genetic disorders that lead to the same or similar clinical features are very heterogeneous, so there are often several subtypes of the same disease that cannot be treated with the same therapy. On the other hand, the costs of developing a new drug, even if it had more favorable conditions by obtaining the status of 'orphan drug', cannot be lower than a certain limit; when development costs are divided by the number of patients on the market, the price of the drug per patient is expected to be very high. With such high prices, even a gain of a few QALY will not help achieve a favorable cost-effectiveness ratio [44]. The problem becomes even more significant when the enzyme therapy is inactivated by antibodies produced by the host, so a multimodal treatment must be applied. Multimodal treatment includes, in addition to enzyme replacement, specific dietary measures, and stem cell transplantation, as is the case with Wolman's disease: the total cost of therapy becomes even higher, and the effect of the treatment does not increase proportionally, so the ratio of costs and effects is even less favorable [45]. In such a situation, hematopoietic stem cell transplantation or bone marrow transplantation appears as a therapeutic alternative with a more favorable cost-effectiveness ratio than ERT, despite the risk of rejection and infection that such therapy carries, as has already been shown for Gaucher's disease in socio-economic conditions prevailing in India [46].

The question is how to resolve this challenging situation, that is, to make the causal therapy of rare hereditary diseases acceptable to the payers of health services, first in developed and then also in less developed and underdeveloped countries of the world. The answer has not been definitively given to date, there is a unanimous consensus that the usual method of assessing the cost-effectiveness of drugs with fixed willingness-to-pay limits cannot be used for the causal therapy of rare hereditary diseases. More than a decade ago, a multicriteria decision-making method was proposed that would take into account several aspects of causal therapy: rarity, the severity of the disease, the availability of alternative therapies, efficacy of the medicine, number of eligible patients, manufacturing complexity, necessary follow-up

Table 3. Value of main output variables in the base case and PSA (mean ± 99%CI).

Output variables	Base case (RSD)	PSA (RSD)
Scenario 1 (velmanase alfa *vs.* no causal therapy)		
ICER	941,587,152 ± 7,265,674	725,326,217 ± 4,922,928
Net monetary benefit	−365,242,595 ± 2,779,403	−368,742,966 ± 2,468,598
Scenario 2 (velmanase alfa *vs.* BMT)		
ICER	−398,412,755 ± 3,305,129	−422,496,475 ± 3,323,374
Net monetary benefit	−357,498,497 ± 2,912,279	−357,960,242 ± 2,762,547
Scenario 3 (BMT *vs.* no causal therapy)		
ICER	6,032,689 ± 69,063	6,528,187 ± 72,915
Net monetary benefit	−6,785,860 ± 101,332	−6,910,375 ± 99,371

measures, etc. [47]. This approach would enable the ranking of orphan drugs on the market, so that health service payers could determine their funding priorities and plan their budgets in a much more precise way, without fear of them becoming insufficient. Other proposals for evaluating the cost-effectiveness of drugs for rare diseases include equity weightings of QALYs based on disease prevalence, risk-sharing between pharmaceutical companies and health insurance funds through 'no cure, no pay' schemes (the price of a drug is reduced if the expected clinical effect is not achieved in a particular patient), reimbursement of a drug only for more severe forms of a disease, or dedicated funding, i.e. establishing separate reimbursement funds for causal therapy of rare diseases [48]. Although some of these proposals have taken root in the most developed countries, sustainable financing of causal therapy for all patients with rare diseases who need it is still an elusive goal. The problem is even greater in less developed and underdeveloped countries, where no method of better evaluating the cost-effectiveness of drugs for rare diseases can provide funds in the budget of health care payers, which simply do not exist.

Limitations

Our study has several limitations that may affect the interpretation of its results. First, the price of velmanase alpha used in the study is not officially approved in Serbia because the drug has not yet received marketing authorization, so it is an anticipation of what the definitive price would be on the Serbian market. We attempted to anticipate the price following the Serbian Rulebook that defines medicine prices. The prices taken into consideration are from more developed European countries, where the drug has an official price, so significant future price variations are not excluded. Second, the long-term effectiveness of velmanase alpha in the treatment of alpha-mannosidosis is not yet known, since the majority of studies lasted no more than 5–6 years. This led to increased uncertainty of time to certain events in the model, which we tried to overcome *via* sensitivity analysis. The lack of Serbian domestic cost-of-illness studies relating to alfa-mannosidosis complications also decreased our model's certainty, as we had to rely on data from other countries.

Conclusions

This analysis showed that from the perspective of the Health Insurance Fund of the Republic of Serbia, treatment with Velmanase alfa is not cost-effective compared to bone marrow transplantation and standard-of-care treatment, but is extendedly dominated by linear combination of the latter two therapeutic options. Bone marrow transplantation can be considered cost-effective compared to standard-of-care treatment if a higher cost-effectiveness threshold of 9 GDP per capita/QALY is taken as acceptable for drugs for rare diseases. To make enzyme replacement therapy for alfa-mannosidosis available to Serbian patients, alternative methods of cost-effectiveness estimation must be implemented by Serbian health authorities and health insurance funds.

Author contributions

Ana Antanasković: conceptualization, data curation, writing—original draft preparation, visualization, investigation, writing—reviewing and editing, resources.

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Disclosure statement

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Data availability statement

The study plan is available at the link: https://osf.io/gs756/. The models used in the study and other materials not contained in the Supplementary File are available to interested readers from the corresponding author, at reasonable request.

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