Cost-utility analysis and budget impact analysis of pegvisomant for the treatment of adult patients with acromegaly in Poland

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Abstract

Background: The aim of this publication was to evaluate the cost-effectiveness and financial consequences of pegvisomant (PEG) in the treatment of adult patients with acromegaly, who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues (SSA) did not normalize IGF-1 concentrations or was not tolerated compared with SSA continuation.

Methods: The Markov model constructed in TreeAge Pro with 45-year time horizon was used in the cost-utility analysis (CUA). Quality adjusted life years (QALY) were used as the measure of effectiveness. CUA was conducted from the perspective of the public payer for health services (Polish National Health Fund, PNHF) and from the patient's and PNHF's perspective. Budget impact analysis was performed in a 3-year time horizon from PNHF's perspective. Two scenarios were compared: "present", without reimbursement of PEG; "new", after reimbursement of PEG.

Results: The cost of gaining an additional QALY by replacing SSA with PEG is equal 742,724 PLN/ 714,800 PLN (172 470 €/ 165 986 €) from PNHF/PNHF+patient perspective. The annual expenditure of the PNHF's budget in the first three years would increase by approximately 11.95 million PLN in the first, 26.39 million PLN in the second and 26.5 million in the third year of PEG reimbursement.

Conclusion: The creation of drug program for acromegalic patients, in which reimbursement of PEG will be provided, will significantly influence the prognosis, course of the disease and improve the patient's quality of life.

Introduction

Acromegaly is a rare, chronic disease caused by excessive production of growth hormone (GH). The most common cause of excessive GH production is pituitary tumor. This leads to changes in the external appearance with the enlargement of: facial skins, hands and feet, as well as the growth of internal organs and bones and many systemic complications that cause significant deterioration of the quality of life and consequently lead to premature deaths. [1] The prevalence of acromegaly varies from 50 to 70 cases per million. The incidence rate is 4 million year (both in Poland and in the world), with the same frequency in both gender. The peak of diagnoses is 40-50 years old. In Poland, approximately 2,000 people suffer from acromegaly.[2, 3] The mortality rate in patients with acromegaly is widely quoted to be 2-2.5 times higher than that of the general population. The untreated patients have a shorter life expectancy of an average 10 years, and mortality from cardiovascular, respiratory and a cancer disease is 2-4 times higher than in the general population.[1, 2]

The main goal of treatment is normalization of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), followed by removal or reduction of pituitary tumor.[1]

Pegvisomant is an analogue of human growth hormone that has been genetically modified to be a growth hormone receptor antagonist. Inhibition of growth hormone action with pegvisomant leads to decreased serum concentrations of insulin-like growth factor-I. [4] In the European Union, pegvisomant is indicate for the treatment of adult patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-1 concentrations or was not tolerated.[4]

Guidelines of the Polish Society of Endocrinology indicate the possibility of using pegvisomant as monotherapy or the use of pegvisomant in combination with somatostatin analogues. In addition, they indicate that the GH receptor antagonist pegvisomant normalize IGF-1 concentration in more than 90% of patients, thus leading to clinical improvement and alleviation of metabolic disorders (increasing insulin sensitivity improves carbohydrate metabolism).[1]

Therapy with an analogue of human growth hormone – pegvisomant in the treatment of acromegaly has already been recommended and reimbursed in most European countries.

The objective of this project was to conduct economic analysis (cost-utility analysis, CUA) and budget impact

analysis (BIA) of pegvisomant for the treatment of adult patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-1 concentrations or was not tolerated compared with SSA continuation as part of drug program. The survey was conducted in accordance with the Polish Agency for Health Technology Assessment and Tariffs (AOTMiT) recommendations.[5]

Material and methods

The decision problem was formulated in accordance with the PICOS scheme (population, intervention, comparator, outcomes, study design) and drug program:

Population: adult patients with acromegaly, who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-1 concentrations or was not tolerated;

Intervention: pegvisomant (PEG), a loading dose of 80 mg should be administered subcutaneously under medical supervision, following this, patients were given pegvisomant at doses of 10 mg daily (dose adjustments should be based on serum IGF-1 levels);

Comparator: continuation of treatment with ineffective somatostatin analogues (SSA);

Outcome: quality-adjusted life years (QALY); impact on the payer's budget;

Study design: head-to-head randomized controlled trials (RCT) conducted in parallel groups. Due to the rarity of the indication, observational studies, including patient records, was the main source of pegvisomant effectiveness.

The exchange rate of Polish National Bank (2018-11-22) was 1€ = 4.3064 PLN.

The size of the target population was calculated on the basis of PNHF data concerning the frequency of high-dose SSA in the treatment of acromegaly, expert opinion and the percentage of patients, who have previously received surgery or radiotherapy [6]. Figure 2 showed the methods of calculating the target population. Based on epidemiologic data, a minimum and maximum estimation variant of the target population was also calculated.

Analytical technique

Due to the statistically significant differences in the response to treatment defined as normalization of serum IGF-1 concentration (main outcome presented in clinical effectiveness assessment of PEG) a cost-utility analysis was performed using the Markov decision model constructed in TreeAge Pro. As the measure of effectiveness, QALY was used and the result was presented as incremental cost-utility ratio (ICUR). ICUR expressed the cost of gaining one additional unit of QALY in case of replacing SSA with PEG.

The BIA calculations were made in an MS Excel® spreadsheet.

Perspective and time horizon

CUA analysis was conducted from the perspective of the public payer for health services (Polish National Health Fund, PNHF) and from the patient and PNHF perspective. Based on the identified economic analyses with similar PICOS, a 20-year time horizon was adopted.[7, 8]

Budget impact analysis was performed in a 3-year time horizon from the perspective of the public payer for health services (PNHF). This assumption is consistent with the AOTMiT guidelines.[5]

Model structure of CUA

In the Markov decision model, the following states, which are important from economic or clinical point of view, were taken into consideration: "IGF-1 normalized", "IGF-1 non-normalized", "discontinuation of pegvisomant therapy" (only the first cycle)" and "death" (Figure 1). For example, in the arm with an available option of using pegvisomant, the patient may start the simulation with an answer to PEG, maintain control of IGF-1 concentration, survive the cycle and start the next with preserved disease control or begin, as a non-responder, in the same cycle to discontinue pegvisomant therapy and die from general causes, thus completing the simulation. The length of the model cycle, corresponding to the frequency of health state changes in patients, is one year. Based on the AOTMiT guidelines a discount rate of 5% for costs and 3.5% for benefits was used.[5]
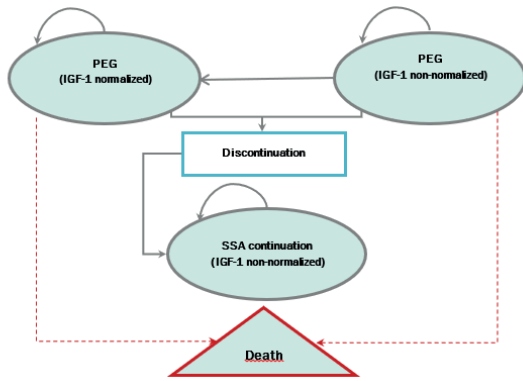
Figure 1. Structure of the model

Assumption and model parameters f CUA

Based on Polish data the mean age of the patients was 52 years and 47.76% were males.[9-12] Data on clinical effectiveness were taken from publications identified as part of the systematic review.[13] Percentages of patients with IGF-1 normalization were calculated from the clinical studies.[14, 15, 16] An annual discontinuation rate of 13.0% was calculated as weighted average percentage of total patient loss based on meta-analysis of studies.[14, 17, 18] The survival of patients was obtained by applying a standardized mortality rate (SMR) to the life table for the general population. SMR for patients with normal IGF-1 was 1.0 and 2.0 for patients with high IGF-1 levels based on meta-analysis of available data.[19, 20, 21]

Based on the data adopted in the Welsh model,[7, 8, 22] the relative change in utility value was calculated (0.7 / 0.81 = 86.4%). It was then used to modify the current, age-dependent utility for the Polish general population,[23] yielding the value corresponding to the group of patients without normalization of concentration IGF-1. In the case of patients responding to PEG treatment, it was assumed that their quality of life returns to the level of the general population (in analogy to that ofConnock 2007), [8] therefore the model used available Polish, age-dependent utility.[23]

Following that, direct medical costs were included: pegvisomant, drug administration, qualification, diagnostic and monitoring, somatostatin analogues (current practice). Prices were evaluated on the basis of Polish National Health Fund regulations applicable in 2018.

According to the drug program description a large loading dose (80 mg) of PEG was administered on day one. In subsequent days, the average dosage in patients with IGF-1 normalization and without IGF-1 normalization was 15.6 mg/day and 16.9 mg/day, respectively (based on large

register of patients with acromegaly (ACROSTUDY)[15]). In Table 1 main parameters used in the model were presented.

Comparable scenarios in BIA

Two future scenarios were estimated: "existing", assuming no reimbursement of pegvisomant and "new", in which PEG receives a reimbursement within drug program in the treatment of acromegaly (it was assumed that all patients qualifying for the drug program will start using the new therapy). The analysis included an open population (according to AOTMiT[5] guidelines). This means that individual patients are included or excluded, depending on whether they currently meet the predefined inclusion criteria. The number of patients with acromegaly initiating treatment and continuing in the subsequent quarterly periods of the program's functioning, including their loss in the first year due to the lack of response to treatment or due to adverse events or mortality in this population, was estimated.

Costs included in BIA

Medical direct costs (pegvisomant, drug administration, qualification, diagnostic and monitoring, somatostatin analogues (current practice). PEG dosing and cost included were analogous to that in economic analysis.

Results

CUA results

Results of a cost-utility analysis of PEG were presented in Table 2. The incremental cost-utility ratio (ICUR) for the comparison of PEG with SSA was determined from the following formula:

The cost of gaining an additional QALY by replacing SSA with PEG is equal 742,724 PLN/ 714,800 PLN (172 470 €/ 165 986 €) from PNHF/PNHF+patient perspective. The cost-utility analysis proved that PEG is more expensive but more effective (1.68 QALY) than SSA continuation in the treatment of adult patients with acromegaly, who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-1 concentrations or was not tolerated.

The results obtained are above the acceptability threshold in Poland (134,514 PLN (31 236 €)).

Table 1. Summary of model parameters		
Parameter	Base case	Sources
Age	52 years	Bałdys-Waligórska 2010 [9], Orlewska 2012 [10], Śliwczynski 2016 [11]
Gender distribution	women: 52.24% men: 47.76%	GUS [12]
Time horizon	20 years	Moore 2009 [7], Connock 2007 [8] /
Discount rate	5% for costs and 3.5% for benefits	[5]
Effects		
Response to treatment (PEG), IGF-1 normalized	62% (95% CI: 59%; 66%)	Meta-analysis of available data: Buhk 2010 [14], ACROSTUDY (Strasburger 2018 [15]), GPOS (Berg 2010 [16])
Discontinuation (PEG)	13% (95% CI: 3%; 29%)	Weighted average percentage of total patient loss based on a meta-analysis (Marazuela 2009 [17], Buhk 2010 [14] oraz Marazuela 2011 [18])
SMR (IGF-1 normalized)	1 (95% CI: 1.0; 1.39)	Meta-analysis of available data:Holdaway 2008 [19], Wu 2010 [20], Mercado 2014 [21]
SMR (IGF-1 non-normalized)	2.00 (95% CI: 1.22; 3.29)	Meta-analysis of available data:Holdaway 2008 [19], Wu 2010 [20], Mercado 2014 [21]
Utility (IGF-1 normalized)	Depends on age for the Polish population	Golicki 2015 [23]
Utility (IGF-1 non-normalized)	Value reduction for patients with response of 13.6%	Based on WMP 2005 [22], Connock 2007 [8], Moore 2009 [7]
Cost and resource utilization		
Dosage of pegvisomant	The initial dose: 80 mg, then on average: patients with IGF-1 normalization: 15.6 mg / day; patients without IGF-1 normalization: 16.9 mg / day	[4], project of drug program, ACROSTUDY (Strasburger 2018 [15])
Cost PEG per cycle (annual cost) - patients with IGF-1 normalization	1 year: 217,411.58 PLN (50,486 €) next years: 214,981.77 PLN (49,921 €)	[4], Strasburger 2018 [15],Manufacturer
Cost PEG per cycle (annual cost) - patients with no IGF-1 normalization	1 year: 235,277.68 PLN (54,634 €) next years: 232,896.91 PLN (54,082 €)	[4], Strasburger 2018 [15],Manufacturer
Costs of qualification	338.00 PLN (78 €)	Polish National Health Fund
Costs of administration, monitoring and diagnostics	108.16 PLN + 1,830.00 PLN (25 € + 425 €)	Polish National Health Fund, project of drug program, calculation
The number of doses SSA	13	[24, 25]
Cost SSA (annual cost)	PNHF perspective: 79,882.45 PLN (18,550€) PNHF+patient perspective: 85,719.71 PLN (19 905 €)	Polish National Health Fund
Costs of monitoring for SSA	702.35 PLN (163 €)	Polish National Health Fund,Orlewska 2012 [10]

CI – confidence interval

Table 2. The results of the cost-utility analysis from 20-year time horizon		
Parameters	PEG	SSA
PNHF perspective		
Total costs	2,124,436.49 PLN (493,321 €)	878,892.63 PLN (204,090 €)
Incremental cost	1,245,543.86 PLN (289,231 €)	
Total health effects (QALY)	10.7495	9.0725
Incremental health effects (QALY)	1.6770	
ICUR	742,724 PLN (172,470 €)	
PNHF+patient perspective		
Total costs	2,141,271.38 PLN(497,230 €)	942,556.31 PLN (218,873 €)
Incremental cost	1,198,715.07 PLN (278,357 €)	
Total health effects (QALY)	10.7495	9.0725
Incremental health effects (QALY)	1.6770	
ICUR	714,800 PLN (165,986 €)	

| Parameter	„Existing" scenario [PLN/€]			„New" scenario [PLN/€]		
	First year	Second year	Third year	First year	Second year	Third year
Cost PEG	0	0	0	18 052 920/ 4 192 114	39 880 927/ 9 260 851	41 234 824/ 9 575 242
Cost SSA	6 426 787/ 1 492 380	15 350 263/ 3 564 523	17 266 520/ 4 009 502	178 516/ 41 454	1 618 876/ 375 923	2 397 114/ 556 640
Costs of qualification	0	0	0	50 134/ 11 642	33 688/ 7 823	4 953/ 1 150
Costs of administration, monitoring and diagnostics	0	0	0	145 751/ 33 845	330 115/ 76 657	348 475/ 80 920
Costs of monitoring for SSA	56 506/ 13 121	134 964/ 31 340	151 812/ 35 253	1 570/ 365	14 234/ 3 305	21 076/ 4 894
Total expenses	6 483 29/ 1 505 502	15 485 227/ 3 595 864	17 418 332/ 4 044 755	18 428 891/ 4 279 419	41 877 840/ 9 724 559	44 006 442/ 10 218 847
Incremental expenses	-	-	-	11 945 598/ 2 773 917	26 392 613/ 6 128 695	26 588 110/ 6 174 092

Table 3. The results of BIA
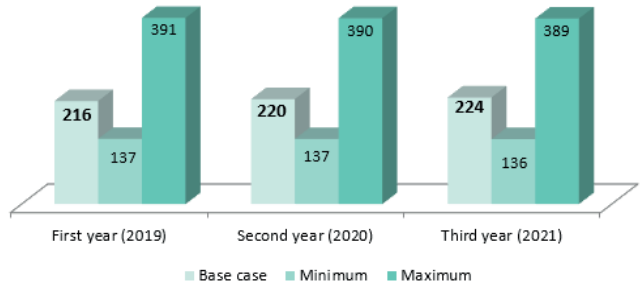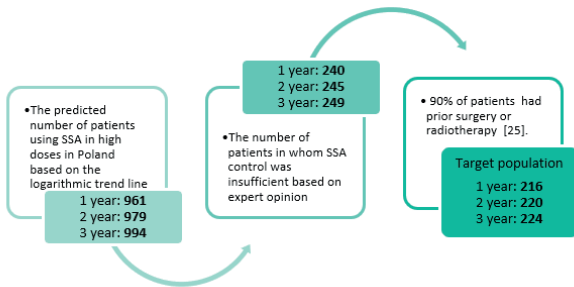
Figure 2. Details of the target population calculation

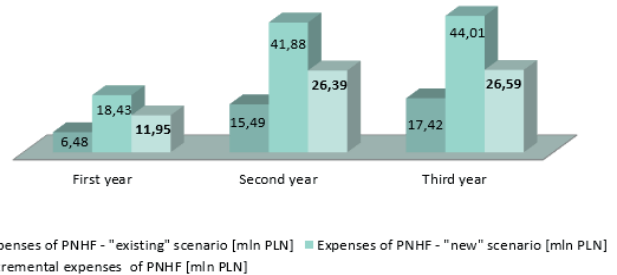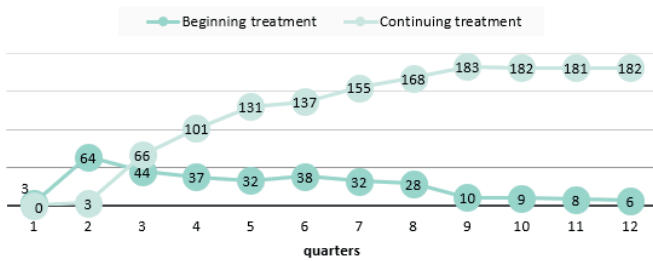
Chart 1. Target population

Chart 2. The flow of patients using PEG as part of a drug program in subsequent quarters of the time horizon

Chart 3. BIA results from PNHF perspective

BIA Results

The estimated number of target population would be around 216 in the first, 220 in the second and 224 in the third year (Chart 1). The flow of patients using PEG as part of a drug program in the subsequent quarters of the time horizon is presented on Chart 2.

In case of reimbursement of PEG for the treatment of acromegaly, the annual expenditure of the PNHF budget in the first three years would increase by approximately 11.95 million PLN in the first, 26.39 million PLN in the second and 26.5 million in the third year of reimbursement (Chart 3, Table 3).

Discussion

Acromegaly is a rare endocrine disease often associated with disfiguring physical symptoms, multiple debilitating comorbidities, an increased rate of mortality and an impaired quality of life.[1-3] Poland is one of the very few countries where patients with acromegaly do not have provided pegvisomant (PEG is refunded in most European countries).[26]

The aim of this publication was to evaluate the cost-effectiveness and financial consequences of the PEG treatment of adult patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-1 concentrations or was not tolerated.

The HTA analyses underlying the article underwent verification by an independent governmental agency (AOTMiT) in terms of methodological correctness and compliance with Polish law. In addition, the analyses were the basis for the reimbursement process which finalised as positive recommendation.

To assess the cost-effectiveness of pegvisomant compared to SSA a decision tree model was prepared (TreeAge Pro). The model was designed to estimate costs and outcomes, in terms of QALY, from the perspective of the PNHS over 20-year time horizon. Similarly to the majority of economic analyses concerning profitability of acromegaly treatment, a Markov model was implemented [7, 8]. The economic model predicted a gain of 1.68 QALY from 9.07 QALY in the SSA arm to 10.75 with PEG. This is a very substantial increase for those patients. Results of the cost-utility analysis proved that a therapy with PEG is more expensive and more effective than SSA. In the absence of special criteria for the assessment of drugs used for rare diseases, this means that PEG is unlikely to represent good value for money when considered against the current standards (SSA) applied to interventions in the Polish Health service.

The results obtained in the analysis were quite similar to the results presented in the other published economic studies for pegvisomant (PEG was above the generally applied cost-effectiveness thresholds). However, it should be noted that the Polish model adopted stricter assumptions regarding the main element of the model (assessment of survival and treatment response) than in the Welsh model. For example, the adoption of the SMR value at the level of the original version of the manufacturer's analysis resulted in obtaining 606 thousand PLN (140 721 €)/ QALY, which is close to the original result, converted into PLN (493 thousand PLN (114 481 €)/ QALY). This proves the crucial importance of assessing the survival of patients with acromegaly for the results of economic analysis.

When considering the economic value of a product, it is important to assess the budget impact. In order to effectively capture all the relevant costs and consequences, guidelines recommend BIA populations to be open,[5] in the sense that individuals can enter or leave the population depending on whether they meet the criteria for inclusion. In this analysis, individual patients are included in the population or excluded, depending on whether they currently meet the defined inclusion criteria. The target populations were calculated based on PNHF data, which was the most reliable and current source of Polish data on the frequency of SSA in high doses in the treatment of acromegaly. Most importantly, PNHF data showed real numbers of patients actually treated. This allows estimating the actual expenditure of the public payer incurred for the implementation of the proposed drug program. The average annual treatment costs were calculated based on the assumption that all patients received a loading dose (80 mg) and an average daily dosage of 15.6 mg /day and 16.9 mg/day for patients with IGF-1 normalization and without IGF-1 normalization, respectively.

The annual expenditure of the PNHF budget in the first three years would increase by approximately 11.95 million PLN in the first, 26.39 million PLN in the second and 26.5 million in the third year of PEG reimbursement.

Conclusions

At the current market price (connected with complicated technological process) pegvisomant is not cost effective, which is common situations in economic evaluation for orphan drugs. Pegvisomant therapy might not offer an

economically beneficial treatment option, despite it has high clinical value for acromegalic patients.

Abbreviations

GH – growth hormone
IGF-1 – insulin-like growth factor 1
CUA – cost-utility analysis
BIA – budget impact analysis
AOTMiT – Polish Agency for Health Technology Assessment and Tariffs
PEG – pegvisomant
SSA – somatostatin analogues
QALY – quality-adjusted life years
RCT – randomized controlled trials
ICUR – incremental cost-utility ratio
PNHF – Polish National Health Fund
SMR – standardized mortality rate

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