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ORIGINAL RESEARCH

Cost Evaluation and Economic Sustainability of Enzyme Replacement Therapies for Fabry Disease in Italy from the Hospital Perspective

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ABSTRACT

BACKGROUND AND AIM: Fabry disease is a rare X-linked lysosomal hereditary disease caused by pathogenic variants in the *GLA* gene that results in deficient α-galactosidase A enzyme activity. Enzyme replacement therapy (ERT) remains a primary approach to address the enzymatic defect and its pathophysiological impacts. This study aimed to evaluate the annual treatment costs associated with agalsidase alfa, agalsidase beta and pegunigalsidase alfa within the context of the Italian National Healthcare Service (NHS).

METHODS: A cost comparison model was developed to estimate the treatment-related expenditure for agalsidase alfa, agalsidase beta, and pegunigalsidase alfa over 1-year time horizon from the hospital perspective. The analysis accounted for drug acquisition and administration costs across hospital-based, home-based, and self-administration settings. Infusion durations were estimated based on product specifications and patient characteristics from published literature. Costs were calculated using adjusted ex-factory list prices and literature-sourced hourly rates for healthcare professionals. Expert validation ensured model accuracy, and sensitivity analyses examined the impact of varying infusion scenarios.

RESULTS: In the base case, agalsidase alfa demonstrated the lowest annual treatment cost (€172,395), followed by pegunigalsidase alfa (€173,744), while agalsidase beta incurred the highest cost (€191,143). Scenario analysis confirmed that agalsidase alfa offers a more sustainable alternative compared to agalsidase beta, while demonstrating comparable costs to pegunigalsidase alfa. Furthermore, the analysis indicated that variations in infusion settings had impact on overall outcomes, depending on the home or hospital preference.

CONCLUSION: This economic evaluation suggests that agalsidase alfa may offer cost advantages relative to other ERTs, particularly in comparison to agalsidase beta. These advantages are primarily driven by lower annual treatment costs. In addition, agalsidase alfa's unique approval for self-administration in Italy, has the potential to reduce healthcare expenditures, optimizing hospital resource allocation, and enhancing the efficiency of healthcare delivery for patients with Fabry Disease.

Keywords

Fabry disease; Enzyme replacement therapy; Cost comparison; Italy

INTRODUCTION

Fabry disease (FD) [OMIM #301500] is a rare, X-linked lysosomal hereditary disorder caused by pathogenic variants in the *GLA* gene [1]. This condition is characterized by severe multisystemic involvement, ultimately leading to major organ failure and premature death [1,2].

Enzyme replacement therapy (ERT) was the first disease-specific treatment developed for FD. In 2001, the European Medicines Agency (EMA) granted marketing authorization to two ERTs, agalsidase alfa and agalsidase beta [3,4]. More recently, in 2023, pegunigalsidase alfa was also approved for the treatment of adult patients with a diagnosis of FD [5].

Although no randomized clinical trials directly comparing agalsidase alfa and agalsidase beta have been conducted, a comprehensive international study [6] assessed clinical and biochemical outcomes associated with these therapies. This study combined retrospective data

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from three European FD centers of excellence with prospectively collected data from the Canadian Fabry Disease Initiative over an 8-year follow-up, involving a total of 387 patients in the analysis. The study concluded that agalsidase beta did not lead to significant differences in clinical events compared to agalsidase alfa. Additionally, the phase III BALANCE study (NCT02795676), a randomized head-to-head clinical trial, evaluated efficacy, safety and tolerability of pegunigalsidase alfa versus agalsidase beta [7]. Over a 2-year period, the trial demonstrated that pegunigalsidase alfa was non-inferior to agalsidase beta in maintaining estimated glomerular filtration rate (eGFR) levels. Furthermore, pegunigalsidase alfa exhibited lower rates of treatment-emergent adverse events and mild or moderate infusion-related reactions.

Although ERTs demonstrate effective clinical outcomes, the need for a lifelong intravenous (IV) administration on a biweekly schedule poeses challenges, interfering with daily life activities and patents' quality of life. Home treatment has emerged as a safe and effective alternative to hospital-based administration, offering a solution to reduce the "treatment burden" with ERT. Evidence indicates that home-based infusions improved treatment adherence and have a significant and positive impact on quality of life [8-13]. Moreover, a recent expert consensus recommended home infusions as a strategy to mitigate therapy-related burdens and enhance patients' quality of life [14].

This analysis aimed to provide a comprehensive comparison of the annual treatment costs associated with agalsidase alfa, agalsidase beta, and pegunigalsidase alfa within the Italian National Healthcare Service (NHS), evaluating both drug acquisition costs and administration expenses from a hospital perspective. The purpose of this analysis is to estimate the economic burden in Fabry Disease considering the potential home-based infusion saving.

METHODS

Cost Analysis Framework and Model Parameters

The analysis focused on the ERTs reimbursed in Italy at the time of the study: agalsidase alfa, agalsidase beta, and pegunigalsidase alfa.

A cost comparison model was developed to calculate the treatment costs associated with each therapy, including both drug acquisition and administration expenses over a 1-year time horizon. The model incorporated different administration settings, considering hospital-based and home-based infusions.

To ensure consistency with the Italian clinical practice, all model inputs and assumptions were validated by clinical practice perspective.

The parameters utilized to inform the model are detailed in the following sections and listed in Table I.

Patient characteristics

In the absence of Italy-specific data, patient characteristics were sourced from a large cohort of patients enrolled in the Fabry Outcome Survey [11], as summarized in Table I. This methodology is consistent with the approach adopted in a previous Italian study [19].

Drug acquisition cost

To estimate drug acquisition costs, ex-factory prices net of mandatory discounts were used, as detailed in Table I. Agalsidase alfa is recommended at a biweekly dose of 0.2 mg/kg, while agalsidase beta and pegunigalsidase alfa are approved at a higher biweekly dose of 1.0 mg/kg. Accordingly, the analysis considered a total of 26 infusions annually, in line with dosing regimens outlined in the respective Summary of Product Characteristics (SmPc) [3-5].

The drug acquisition cost per infusion was determined based on the price per pack and the estimated vial consumption. Due to the weight-dependent nature of dosing regimens, vial consumption was estimated by modeling patient weight using a normal distribution, with mean and standard deviation as reported in the literature [11]. Vial sharing was not considered from this analysis to ensure constancy in cost estimation. To assess the impact of patient weight, we calculated annual treatment costs for fixed body weights ranging from 35.5 kg to 105 kg. The analysis was based on approved weight-based dosing and estimated vial use per infusion. Results are reported in Supplementary Table I.

Infusion time and administration setting

Infusion times, as outlined in Table I, were estimated based on the recommendations provided in the respective SmPC and the distribution of patient weight. In the absence of specific

Model input	Base-case value	Reference
Patient characteristics		
Females (%)	51.9	[11]
Mean weight for males (kg [SD])	66.3 (19.5)	[11]
Mean weight for females (kg [SD])	64.2 (17.8)	[11]
Drug acquisition cost – price per pack (€)		
Pegunigalsidase alfa	1,758.67	[15]
Agalsidase beta	3,077.67	[16]
Agalsidase alfa	1,538.84	[17]
Infusion time – mean time per infusion (min)		
Pegunigalsidase alfa	125	Estimated from BRIDGE trial [20]
Agalsidase beta	271	Estimated from SmPC and patients weight distribution [4]
Agalsidase alfa	40	Estimated from SmPC [3]
Infusion setting (%)		
Pegunigalsidase alfa		
• Hospital infusion	95	Expert opinion
• Home infusion	5	Expert opinion
• Self-administration	N/A	
Agalsidase beta		
• Hospital infusion	50	Expert opinion
• Home infusion	50	Expert opinion
• Self-administration	N/A	
Agalsidase alfa		
• Hospital infusion	50	Expert opinion
• Home infusion	50	Expert opinion
• Self-administration	0	Expert opinion
Home infusion provided by the Company (%)		
Pegunigalsidase alfa	95	Expert opinion
Agalsidase beta	95	Expert opinion
Agalsidase alfa	95	Expert opinion
Drug infusion cost (€/h)		
Physician hourly cost)	60.03	[18]
Nurse hourly cost	28.25	[18]
Hospital infusion (%)		
Physician time during infusion	20	Expert opinion
Nurse time during infusion	80	Expert opinion
Home infusion (%)		
Physician time during infusion	-	Expert opinion
Nurse time during infusion	100	Expert opinion
Self-administration (h)		
Physician time for training	3.33	Expert opinion
Nurse time for training	3.33	Expert opinion

Table I. *Model parameters*
SmPC: summary of product characteristics; SD: standard deviation

information, the mean infusion time for pegunigalsidase alfa was derived using data from the BRIDGE study (NCT03018730) [20].

Regarding the infusion setting, three options were considered in the model: hospital-based infusion, home infusion, and self-administration. For each therapy, the distribution of infusion settings, as reported in Table I, was estimated based on expert clinician point of view to reflect Italian clinical practice.

Self-administration is currently approved exclusively for agalsidase alfa. Insights from the clinical expert indicate that no patients are currently undergoing treatment using this method. To investigate this possibility, a hypothetical scenario was developed as part of the sensitivity analysis to evaluate the potential impact of patient treatment via self-administration.

Drug infusion cost

In the analysis, infusion costs were determined based on infusion duration. For home-based infusions, the model assumed that, in Italy, most infusions are provided by the pharmaceutical companies, as reported in Table I. In such cases, the infusion cost is included within the drug cost, as ERT is administered by a nurse employed by the pharmaceutical company.

As specified in Table I, hourly costs for physicians and nurses were obtained from published literature [18]. For both hospital-based and home infusions, the duration of physician and nurse involvement in ERT infusion was informed by expert opinion to reflect the Italian clinical practice. For home-based infusions, it was assumed that physicians were not involved. For self-administration, a one-time training cost was included into the analysis to account for the preparation and education training provided to the patient and/or caregiver prior to initiation. This cost was estimated based on the assumption of 10 training sessions, each lasting 20 minutes, conducted by both a physician and a nurse.

Scenario analysis

A series of scenarios was investigated to test the robustness of base-case results.

To account for the different regional contexts across Italy, we investigated a scenario where all home infusions were provided by pharmaceutical companies and a scenario where home infusions were not provided by pharmaceutical companies. We also explored a scenario where all infusions were provided in the hospital. Regarding agalsidase alfa, we investigated a scenario where all home infusions were self-administration.

Cost item[1] (€)	Pegunigalsidase alfa	Agalsidase beta	Agalsidase alfa
Drug cost	171,960	189,028	172,083
Administration cost	1,784	2,155	312
Total cost	**173,744**	**191,143**	**172,395**

Table II. *Base-case results: breakdown by cost item*
[1] The costs refer to a total of 26 infusions (biweekly infusions)

Infusion setting[1] (€)	Pegunigalsidase alfa	Agalsidase beta	Agalsidase alfa
Hospital infusion	165,142	96,546	86,341
Home infusion	8,602	94,597	86,054
Self-administration[2]	N/A	N/A	-
Total cost	**173,744**	**191,143**	**172,395**

Table III. *Base-case results: breakdown by infusion setting*
[1] The costs refer to a total of 26 infusions (biweekly infusions)
[2] Self-administration is currently approved exclusively for agalsidase alfa; however, no patients are currently receiving treatment using this method

Parameter	Investigated scenarios	Total costs (€)		
		Pegunigalsidase alfa	Agalsidase beta	Agalsidase alfa
Base case		173,744	191,143	172,395
Home infusion provided by pharmaceutical companies	All home infusions provided by pharmaceutical companies	173,740	191,060	172,383
	No home infusions provided by pharmaceutical companies	173,817	192,718	172,628
Infusion setting	All hospital-based infusions	173,834	193,092	172,683
Infusion setting for algasidasi alfa	Hospital: 50% Self-administration: 50%	173,744	191,143	172,677

Table IV. *Scenario analysis results*

RESULTS

The annual treatment costs were estimated at €172,395, €191,143, and €173,744 for agalsidase alfa, agalsidase beta, and pegunigalsidase alfa, respectively. Across all the ERTs considered, drug costs accounted for most of the treatment cost, as detailed in Table II. Table III reports the breakdown of results by infusion setting.

As shown in Table IV, the scenario analysis confirmed the base-case findings, identifying agalsidase alfa as a more sustainable therapeutic option in comparison to agalsidase beta, while exhibiting comparable cost with pegunigalsidase alfa. Across all investigated scenarios, model outcomes remained stable, as drug acquisition costs consistently emerged as the key driver.

DISCUSSION

This analysis examined the annual treatment costs associated with agalsidase alfa, agalsidase beta, and pegunigalsidase alfa in patients with FD within the context of the Italian NHS. The evaluation considered both drug costs and administration costs, adopting a hospital perspective. This perspective was selected as it reflects the decision-making level where treatment procurement and resource allocation typically occur. Hospitals are directly responsible for the acquisition and administration of therapies, making drug and administration costs the most relevant and actionable components for budget impact evaluations.

In the base case, agalsidase alfa emerged as the most sustainable treatment option, with an estimated mean annual cost of €172,395. Pegunigalsidase alfa was associated with a slightly higher annual cost of €173,744, while agalsidase beta was found to be the most expensive ERT, with an annual cost of €191,143. Scenario analyses also confirmed the robustness of the base-case results.

These findings are consistent with a previous study by Silvola et al. [19], that compared the treatment costs of agalsidase alfa and agalsidase beta. That study concluded that the use of agalsidase alfa offered both economic and organizational advantages, allowing for improved optimization and efficiency in the treatment of FD patients in Italy. The current analysis builds upon this comparison by incorporating pegunigalsidase alfa, further broadening the scope of cost evaluation and providing a more comprehensive perspective.

This analysis presents some limitations, primarily due to the scope and data availability. The model focused only on drug acquisition based on list prices and administration costs for an average patient, without accounting for variables such as comorbidities, disease severity, or other disease-related factors. These factors were excluded due to limited consistent data across treatments and to maintain comparability. Infusion times and settings were estimated as yearly averages, and potential switches between therapies were not included. These simplifications reflect standard practice and were necessary to avoid overcomplicating the model with highly individualized scenarios. Furthermore, the model did not assess improvements in quality of life, despite the expectation that both home infusions and self-administration could enhance patient quality of life. Patient preferences were also excluded from the analysis; however, it is reasonable to assume that many patients might favor the shorter infusion time. Additionally, other direct healthcare costs, such as specialist visits, diagnostic tests, hospitalizations, and additional treatments related to the disease or therapy, and indirect societal costs, such as absenteeism from work and patient-incurred expenses, were also excluded, potentially underestimating the broader impact of treatment choices on societal and economic outcomes. Including them would require a broader societal approach and access to real-world data not available for this study.

The BRIGHT study (NCT03180840) recently investigated the pharmacokinetics, safety, and efficacy of pegunigalsidase alfa at a dose of 2 mg/kg administered every four weeks [21]. Currently, this dosing is not reimbursed in Italy and therefore, it was not possible to include this option in the analysis.

CONCLUSIONS

This economic analysis suggests that agalsidase alfa may offer cost advantages relative to other ERTs, particularly in comparison to agalsidase beta. These advantages are primarily driven by lower annual treatment costs and agalsidase alfa's unique approval for self-administration in Italy, which has the potential to reduce treatment expenditures, optimize hospital resource allocation, and enhance the efficiency of healthcare delivery for patients with Fabry

Disease. While the analysis focused on treatment expenditure (specifically drug and administration costs) and did not include broader healthcare or societal costs, it provides relevant insights for hospital-level decision-making. Future research incorporating patient preferences, quality-of-life outcomes, and long-term clinical benefits could offer a more comprehensive evaluation of the overall value of ERTs across different healthcare settings.

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Conflicts of Interest

GG is an employee of AdRes HEOR, which has received project funding from Takeda for this analysis. ES, LA, and RV are employees of Takeda but do not hold any stock options. MS has received honoraria from Sanofi, Takeda, and Chiesi for participation in advisory boards and for speaking engagements.

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