Burden of illness of Pompe disease in patients only receiving supportive care

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Abstract

Background Pompe disease is an orphan disease for which enzyme replacement therapy (ERT) recently became available. This study aims to estimate all relevant aspects of burden of illness—societal costs, use of home care and informal care, productivity losses, and losses in health-related quality of life (HRQoL)—for adult Pompe patients only receiving supportive care.

Methods We collected data on all relevant aspects of burden of illness via a questionnaire. We applied a societal perspective in calculating costs. The EQ-5D was used to estimate HRQoL.

Results Eighty adult patients (87% of the total Dutch adult Pompe population) completed a questionnaire. Disease severity ranged from mild to severe. Total annual costs were estimated at €22,475 (range €0–169,539) per adult Pompe patient. Patients on average received 8 h of home care and 19 h of informal care per week. Eighty-five percent of the patients received informal care from one or more caregivers; 40% had stopped working due to their disease; another 20% had reduced their working hours.

HRQoL for Pompe patients who only received supportive care was estimated at 0.72, 17% lower than the Dutch population at large.

Conclusions Adult Pompe disease is associated with a considerable burden of illness at both the societal and patient levels. The disease leads to substantial costs and dependency on medical devices, home care, and informal care, and has a high impact on the patient’s social network. In addition, patients are limited in their ability to work and have significantly reduced HRQoL.

Introduction

Pompe disease (glycogen storage disease type II; acid maltase deficiency) is a neuromuscular and lysosomal storage disorder caused by deficiency of the enzyme acid alpha-glucosidase, which is required for the degradation of lysosomal glycogen (Hirschhorn and Reuser 2001). Storage of glycogen occurs mainly in skeletal muscles and leads to loss of muscle function. The disease presents as a broad clinical spectrum. The severe classic infantile form is
rapidly progressive and leads to death within the first year of life (van der Ploeg and Reuser 2008; van den Hout et al. 2003; Kishnani et al. 2006). The majority of patients have a more slowly progressive or “late-onset” form of the disease. First symptoms may present from infancy to the sixth decade of life. The vast majority of patients are adults. Muscle weakness affects both mobility and respiratory function, and most patients eventually become wheelchair-bound or ventilator-dependent (van der Ploeg and Reuser 2008; Laforet et al. 2000; Hagemans et al. 2005).

Pompe disease is an orphan disease, which is defined in Europe as a disease that affects fewer than 5 per 10,000 people and in the U.S. as a disease that affects fewer than 200,000 people. Pompe disease occurs with an estimated frequency of approximately 1 in 40,000 births in the Netherlands (Ausems et al. 1999). Similar or lower frequencies have been reported for other countries (Martiniuk et al. 1998; Meikle et al. 1999). Our study focuses on adult Pompe disease patients, who make up about 80% of the known Dutch patient population.

In 2006 the commercial availability of enzyme replacement therapy (ERT) made Pompe disease the first inheritable muscle disorder for which therapy is available (van den Hout et al. 2000; Kishnani et al. 2007; van der Ploeg et al. 2010). For a few other lysosomal storage disorders (Gaucher disease, Fabry disease, mucopolysaccharidosis I, II, and VI), similar therapies became available at earlier stages (Barton et al. 1991; Eng et al. 2001; Schiffmann et al. 2001; Kakkis et al. 2001; Harmatz et al. 2004). Costs of ERT in Pompe disease are considerable, especially in adults, averaging about €300,000 per patient annually. In the Netherlands ERT for Pompe disease is conditionally reimbursed for a period of 3–4 years. Traditional cost-effectiveness analysis is considered inappropriate for orphan diseases because of their low frequencies and relatively high developmental costs of treatment (Drummond et al. 2007). Cost-effectiveness is, however, a topic that should be addressed given the conditions of reimbursement of ERT.

Most cost of illness studies, often performed from a societal perspective, fail to account for the entire burden of an illness. Patients might need medical devices; they might need home care and informal care (which can potentially also affect patients’ families’ lives); patients’ capacity to work could be limited; and any disease can affect patients’ health-related quality of life (HRQoL). A burden of illness (BOI) study, which compiles all these aspects, has heretofore been unavailable for adult Pompe disease patients, although BOI of adults with Pompe disease is expected to be substantial. Hence, the aim of this study is to assess the burden of Pompe disease with respect to all aspects: societal costs, the use of home care and informal care, productivity losses, and losses in HRQoL. Following Hagemans et al. (2004), quality of life is expected to be lower for more severely affected patients, i.e., patients using ambulatory or respiratory devices. These patients are also expected to incur higher annual costs.

Methods

Study population

The Center for Lysosomal and Metabolic Diseases at Erasmus Medical Center serves as the national referral center for patients with Pompe disease. From January 2005 to October 2009, 92 adults with Pompe disease were seen at Erasmus MC. This study focuses on patients that only receive supportive care, i.e., costs of ERT are not assessed in this study. Patients who completed one or more health economic questionnaire(s) while only receiving supportive care from January 2005 to October 2009 were included in the sample.

Data collection

As part of a long-term follow-up study on the natural course of the disease, effects of ERT, and health economic aspects, patients were asked to complete a health economic questionnaire every 6 months. All relevant aspects of BOI—medical consumption (e.g., hospital admissions and day visits, ambulatory care, medications, tests, use of medical devices), use of informal care and home care, productivity losses due to absence from work, reduced efficiency, and HRQoL—were considered in the questionnaire. The part of the questionnaire measuring health care utilization contained the most relevant medical services for patients with Pompe disease. No distinction was made between costs related to Pompe disease and those not specifically related to Pompe disease. A similar approach was taken for the assessment of productivity losses.

Data collection started in 2005 and is ongoing for both patients receiving supportive care only and patients receiving ERT. The study was approved by the Central Committee on Research Involving Human Subjects in the Netherlands, and participants provided written informed consent.

Medical costs

Costs were calculated following the Dutch guidelines for costing studies (Oostenbrink et al. 2004). Individual costs were obtained by multiplying volumes of components at individual patient levels with relevant unit costs from the costing manual (Oostenbrink et al. 2004). We adopted the societal perspective, i.e., all relevant costs were included in the analyses regardless of who incurred these costs (Drummond et al. 2004). Home care was valued with wage rates from the Dutch costing manual (Oostenbrink et al.
2004). Medication prices were obtained from the Dutch Pharmacotherapeutic Compass (Health Care Insurance Board 2009). Market prices were used as unit prices for medical equipment, medical devices, and home adjustments. Unit costs are given in Table 1. Semi-annual costs were calculated for each patient by taking the average costs of all observations during the period when the patient did not receive ERT. Semi-annual costs were then doubled to obtain yearly costs per patient. Consumer price indices were used to estimate all costs in 2009 euro values.

Nonmedical costs

Informal care

Informal care was valued using the shadow price method, which uses professionals’ wage rates to valuate informal caregivers’ time.

Productivity losses

Patients might be forced to reduce their working hours or stop working altogether due to disability. The disease might also lead to absences from work. All these aspects were included in the analyses. Costs associated with productivity losses were computed using the friction cost method as recommended in the Dutch guidelines for costing studies (Oostenbrink et al. 2004). In this approach, societal production losses are limited to short-term productivity losses. For absences longer than 22 weeks, an absent employee is assumed to be replaced by a previously unemployed person. The period required to hire and train the new employee is called the friction period, which is the only time associated with productivity costs (Koopmanschap et al. 1995). For (international) comparison, we also applied the human capital approach, which assumes that productivity losses are generated until retirement (van den Hout 2010). Wage rates, corrected for age and gender, were obtained from the costing manual (Oostenbrink et al. 2004).

Health-related quality of life

HRQoL was assessed using the EQ-5D instrument, which consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each having three levels (no limitations, some limitations, and severe limitations). When combined with health states “unconscious” and “death” the instrument describes 245 distinct health states. Each health state is associated with a utility using a scoring formula (Drummond et al. 2004). Utility scores were estimated using the Dutch tariff (Lamers et al. 2006). As such, utilities derived from health states can be regarded as a valuation of that specific health state by the Dutch general population. Utilities typically range from zero (death) to 1 (perfect health). Some health states correspond to negative utilities, implying that these health states are regarded as being worse than death (Lamers et al. 2006).

Statistical methods

Respiratory support and ambulatory support were used as indicators of disease severity (Laforet et al. 2000; Hagemans et al. 2004, 2005). Changes in use of such support over time were examined with McNemar’s test. Year of diagnosis was used to determine disease duration. In comparing utilities and costs, patients were categorized on the basis of their last observation. Differences in utilities and total costs between users and nonusers of ambulatory and respiratory support were examined with Mann-Whitney tests. To examine differences in utilities due to disease duration, patients were

Table 1 Medical cost components and associated unit costs (2009 prices)

| Cost component       | Cost per unit a (€) | Source                                  |
|----------------------|---------------------|-----------------------------------------|
| Hospital care        | 394                 | Oostenbrink et al. 2004                 |
| Intensive care       | 1,847               | Oostenbrink et al. 2004                 |
| Nursing home         | 226                 | Oostenbrink et al. 2004                 |
| Ambulatory care      |                     |                                         |
| Hospital day visits  | 69 b                | Oostenbrink et al. 2004                 |
| GP visits            | 22                  | Oostenbrink et al. 2004                 |
| Physiotherapy        | 25                  | Oostenbrink et al. 2004                 |
| Other paramedical    | 14–91               | Oostenbrink et al. 2004                 |
| Home care per hour   | 29–65               | Oostenbrink et al. 2004                 |
| Medication           |                     |                                         |
| Other medical costs  |                     |                                         |
| Tests and procedures | 54–181              | Oostenbrink et al. 2004                 |
| Respiratory support per day | 5 | Hoogendoorn et al. 2004 |
| Medical devices      | 18–1,500            | Market prices                           |

a Costs per unit are based on average unit costs for medical procedures, consultations, and admissions (Oostenbrink et al. 2004)

b Weighted average of academic and general hospital costs
divided into three groups. Differences in utilities between these groups were examined using Kruskal-Wallis tests. The level of significance for statistical tests was set at 5%. To examine the relation between costs and HRQoL, a Spearman’s correlation was computed. Statistical analyses were performed using Microsoft Excel 2003 (Microsoft, 2003) and SPSS version 15.0 (SPSS, 2006).

Results

Patient population

Eighty adult Pompe patients (87% of the Dutch Pompe population) completed at least one health economic questionnaire while only receiving supportive care. In total, 161 questionnaires were completed. Patient characteristics are presented in Table 2. The average baseline age of the population was 51 years; half of the population was male. The average disease duration at baseline was 9 years. The number of patients using respiratory support and ambulatory support increased during the study, but not significantly (McNemar’s P = 1.000 and P = 0.125, respectively, Table 2). Background information on ambulatory and respiratory support for the 12 patients who did not participate in the study showed no significant differences compared to participating patients.

Medical costs

Table 3 shows the volumes of medical consumption for adult Pompe patients only receiving supportive care. Patients annually made five outpatient hospital visits on average, primarily to the neurologist (28%). Three patients lived permanently in a nursing home due to Pompe disease. On average, patients made two visits to the general practitioner. Physiotherapy was the most frequently used type of paramedical care, averaging 18 visits per patient annually, but its use varied widely among patients. Half the population used medication, taking four different medicines on average. Most patients (70%) reported using medical devices, of which the majority (75%) used more than one device (on average three devices per patient). Most frequently used devices were wheelchairs and other ambulatory support equipment. Thirty-three percent of the patients used respiratory support. Patients’ average need for home care was 8 h/week.

Table 3 also shows the distribution of costs of different medical components. Annual medical costs per patient were estimated at €13,679 (range €0–167,935). Home care, associated with an annual cost of €7,011 (range €0–85,987), was the largest medical cost component (51%). Nursing home admissions—relevant for three patients—accounted for 19% of medical costs. Respiratory support was calculated by multiplying daily costs by 365 days and the percentage of patients using the support. Respiratory support accounted for average annual costs of €574 per patient. Volumes are also presented in Table 3.

Nonmedical costs

Table 4 shows the indirect (nonmedical) costs associated with Pompe disease for patients only receiving supportive care and how these indirect costs relate to medical cost components.

Informal care

Patients on average received 19 h/week of informal care, totaling €5,741 annually (range €0–36,037). Informal care mostly comprised household activities such as cleaning and grocery shopping (44%). Eighty-five percent of the patients received informal care, in most cases from more than one caregiver. Caregivers were most often the patient’s spouse (76%), followed by children (34%), friends (18%), and parents (16%).

Productivity losses

Thirty-nine percent of the patients (n = 31) were employed, 52% of whom indicated they were working fewer hours than they would have without the disease (average: 14 h
fewer). In addition, 32% were absent from work due to illness for an average of 12 work days. Thirty-two patients (40%) indicated they stopped working due to Pompe disease; 11 of them had been declared unfit for work.

| Table 3 | Average medical consumption and average costs per patient for adult Pompe patients only receiving supportive care |
|---------|--------------------------------------------------------------------------------------------------------------------------------|
|         | Respondents using service, n (%) | Average units used per patient, n (SD) | Average annual cost per patient (€) (n=80) | Range of per patient costs (€) |
| Hospital care |                                     |                                         |                                         |                                |
| Patients hospitalized | 12 (15) |                                         |                                         |                                |
| Number of hospitalizations (if hospitalized) | 2 (1.2) |                                         |                                         |                                |
| Duration per hospitalization (nights) | 4 (4.4) |                                         |                                         |                                |
| Intensive care |                                     |                                         |                                         |                                |
| Patients hospitalized | 7 (9)  |                                         |                                         |                                |
| Number of hospitalizations (if hospitalized) | 2 (1.1) |                                         |                                         |                                |
| Duration (nights; if hospitalized) | 5 (3.3) |                                         |                                         |                                |
| Nursing home | 3 (4) | 2,571 | 0–82,454 |
| Ambulatory care | Hospital day visits | 71 (89) | 5 (6.1) | 372 |
| GP visits | 46 (58) | 2 (1.9) | 36 |
| Physiotherapy | 32 (40) | 18 (39.2) | 473 |
| Other paramedical | 27 (34) | 4 (9.7) | 162 |
| Total costs | 1,043 | 0–7,217 |
| Home care | 31 (39) | 7,011 | 0–85,987 |
| Home care (h/week) | 8 (18.4) | 198 | 0–1,257 |
| Medication | Patients on medication | 42 (53) | 4 (3.8) | |
| Number of medicines (if on medication) | 42 (53) | 4 (3.8) | |
| Other medical costs | Tests and procedures | 71 (89) | 7 (4.3) | 750 |
| Respiratory support | 26 (33) | 574 |
| Medical devices | 56 (70) | 411 |
| Number of devices (if using devices) | 56 (70) | 411 |
| Total costs | 1,735 | 0–5,020 |
| Overall | 13,679 | 0–167,935 |

| Table 4 | Estimated annual costs of Pompe disease per adult patient |
|---------|----------------------------------------------------------------|
| Cost category | Average per patient cost (€) | Ranges of per patient costs (€) |
| Hospital days | 313 | 0–6,303 |
| Intensive care | 808 | 0–18,467 |
| Nursing home | 2,571 | 0–82,454 |
| Ambulatory care | 1,043 | 0–7,217 |
| Home care | 7,011 | 0–85,987 |
| Medication | 198 | 0–1,257 |
| Other medical costs | 1,735 | 0–5,020 |
| Total medical costs | 13,679 | 0–167,935 |
| Informal care | 5,741 | 0–36,037 |
| Transportation | 158 | 0–1,918 |
| Productivity losses | 2,633 | 0–38,176 |
| Other nonmedical costs | 263 | 0–7,032 |
| Total nonmedical costs | 8,796 | 0–46,992 |
| Overall | 22,475 | 0–169,539 |

*Including tests, procedures, respiratory support, medical devices*
Using the friction cost method, productivity losses were estimated at €2,633 (range €0–38,176) per patient per year.

Using the human capital approach to assess productivity losses, average annual costs accumulated to €40,590 (± 45,574), 51% of which were due to productivity losses. Total productivity losses until retirement would accumulate to over €200,000 per patient.

Total costs for adult Pompe patients only receiving supportive care accumulated to €22,475 per year (range €0–169,539). Medical costs accounted for 61% of total annual costs. The largest cost components were home care (31%), informal care (26%), and productivity losses (12%).

Health-related quality of life

Seventy-two patients (78% of the Dutch adult Pompe population only receiving supportive care) completed the EQ-5D. Table 5 shows the HRQoL of patients with Pompe disease subdivided by disease duration, ambulatory support, and respiratory support. The average utility for Pompe patients was 0.72, whereas the mean utility for a representative sample of the Dutch population has been estimated at 0.87 (Stolk et al. 2009). The utility decrement as a consequence of Pompe disease of 0.15 was significant. Adult Pompe patients had a 17% lower utility than an average Dutch person. The decrement resulted mainly from mild limitations in the domains of mobility, usual activities, and pain. Severe limitations were only observed in a limited number of cases.

Disease severity was determined on the basis of the use of ambulatory and respiratory support. Patients using ambulatory and respiratory support reported lower HRQoL compared to patients without such devices, but the differences were not significant. In contrast, total costs were significantly higher for patients using ambulatory and/or respiratory devices. Longer disease duration resulted in higher annual costs. The association between disease duration and total annual costs or utilities was not significant. As expected, total annual costs per patient were significantly negatively correlated with HRQoL (rho = −0.534).

### Discussion

This is the first burden of illness study of adults with Pompe disease. The study shows that the disease poses a substantial burden on patients, their families, and society in terms of costs of illness, use of medical devices, home care and informal care, productivity losses, and HRQoL. Costs due to Pompe disease for patients that only receive supportive care amount to an average of €22,475 per patient annually, ranging from €0 to 169,539. Besides costs to society, patients’ daily lives are substantially affected. Indicative is the large number of hours of support patients require from professionals and their social environment. Home care is used on average 8 h/week per patient and accounts for 31% of total annual costs. In addition, patients require 19 h/week of informal care, accounting for 26% of annual costs. Eighty-five percent of the patients receive informal care from one or more caregivers, indicating that the disease also has an important impact on the patient’s social network. Most patients (70%) use medical devices; the majority (75%) of those patients use more than one device. The impact on productivity is considerable. Forty percent of the adult Pompe patients had stopped working due to their disease; another 20% had reduced the number of working hours. Six patients (19% of working patients) indicated they would have applied for a job at a higher functional level if they had not been affected by the disease. The study also shows that HRQoL for patients is estimated at 0.72, an average 17% lower than the Dutch population at large. Lower utilities were associated with higher patient costs.

The highest costs were incurred by patients living in nursing homes with utilities below 0.4 and involved severely affected patients who were both ventilator- and wheelchair-dependent. Only one 20-year-old male patient had zero costs and a utility of 1.

There were no data available on medical costs associated with MRI and DNA testing and home mechanical ventilation. Consequently, medical costs could have been underestimated. In addition, 58% of the working patients indicated they would be more efficient (on average 32%) absent their disease. For some of the patients who had stopped working, corresponding productivity losses could

| Table 5 | HRQoL and total costs for adult Pompe patients only receiving supportive care |
|---------|-----------------------------------------------------------------------------|
|         | Number (%) | EQ-5D utility score (SD) | Number (%) | Total costs (€) |
| Overall (SD; min–max) | 72 | 0.72 (0.18; 0.17–1.00) | 80 | 22,475 |
| Disease duration | | | |
| ≤5 years | 31 (43) | 0.74 (0.15) | 33 (42) | 13,922 |
| 6–15 years | 18 (25) | 0.70 (0.16) | 19 (24) | 26,290 |
| >15 years | 22 (31) | 0.69 (0.23) | 27 (34) | 30,736 |
| Ambulatory support | 37 (51) | 0.67 (0.21) | 44 (55) | 33,246 |
| Respiratory support | 20 (28) | 0.61 (0.26) | 25 (32) | 41,485 |
not be estimated due to lack of data; productivity losses are thus underestimated.

As recommended by the Dutch guidelines for costing studies (Oostenbrink et al. 2004), we applied the friction cost method as the primary approach to assess productivity costs in Pompe patients. Average productivity costs using this method are €2,633 (range €0–38,176) per patient per year, but would have been substantially higher (€40,590 per patient per year; range €0–224,205) had we used the human capital approach. As Pompe disease is a chronic condition, the large difference between the estimates is caused by absence from work due to the disease for a period longer than 22 weeks, which is not associated with costs using the friction cost method. Koopmanschap et al. (1995) argue that the friction cost method is the most realistic approach to value productivity losses in terms of societal costs since a person unable to work for a period of more than 22 weeks will be replaced.

Due to the relatively small number of patients, the uncertainty surrounding the estimates is large, as revealed by the broad ranges of costs and HRQoL estimates. Excluding the three patients permanently living in a nursing home reduced the average annual costs per patient by €3,435 (standard deviation 23%). The impact of the three patients on total costs and standard errors reflects the major problem of dealing with a small patient population in a rare illness such as Pompe disease. This study used information over a period of almost 5 years instead of 1 to increase the number of observations. Such an approach—averaging all observations per patient to enlarge the study population—can be used as a tool to investigate the burden of illness in other rare diseases.

For adult Pompe patients only receiving supportive care, costs associated with informal care and productivity losses account for 26 and 12% of total annual costs of €22,475, respectively. In comparison, total medical and nonmedical annual costs for Dutch patients with multiple sclerosis have been estimated at €17,450 (2009 prices), with productivity losses estimated at 4–5% and informal care about 21% (Kobelt et al. 2006) of the total. For patients suffering from rheumatoid arthritis, informal care and productivity losses have been estimated at 25 and 18% of total annual costs, respectively (Franke et al. 2009). For the Netherlands no cost of illness study was available for a neuromuscular disorder similar to Pompe disease. For the U.S., total annual medical costs for children and young adults with muscular dystrophy were estimated at €18,250 (conversion rate $1 = €0.822; 2009 prices). Costs of informal care and productivity losses were not provided in this study (Ouyang et al. 2008). Transferability of cost of illness estimates is generally limited due to specifics of national health care systems (Drummmond et al. 2005). To increase transparency of the results, volumes and unit costs are also presented in Tables 1 and 3.

For adult Pompe patients who only receive supportive care, HRQoL is 0.72. By comparison, hearing complaints have been associated with an HRQoL of 0.86 (Grutters et al. 2007), and multiple sclerosis with an HRQoL of 0.61 (Kobelt et al. 2006). These figures represent average levels of HRQoL. Large variations in disease severity, however, make HRQoL comparisons between different diseases difficult.

Here we have focused on adult Pompe patients who only receive supportive care. Future studies will similarly examine the burden of illness for adult Pompe patients receiving enzyme therapy to evaluate the cost-effectiveness of enzyme replacement therapy.

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Conflict of interest As of August 2004, A.T.v.d.P. provides consulting services for Genzyme Corp, Cambridge, MA, USA, under an agreement between Genzyme Corp and Erasmus MC, Rotterdam, the Netherlands. This agreement also provides financial support for Erasmus MC for research in Pompe disease. Erasmus MC and inventors for the method of treatment of Pompe disease by enzyme replacement therapy receive royalty payments pursuant to Erasmus MC policy on inventions, patents, and technology transfer.

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References

Ausems MGEM, Verbiest J, Hermans MMP et al (1999) Frequency of glycogen storage disease type II in the Netherlands: implications for diagnosis and genetic counseling. Eur J Hum Gen 7:713–716
Barton NW, Brady RO, Dambrosia JM et al (1991) Replacement therapy for inherited enzyme deficiency: macrophage-targeted glucocerebrosidase for Gaucher’s disease. N Engl J Med 324:1464–1470
Drummmond MF, O’Brien B, Stoddart GL, Torrance GW (2004) Methods for the economic evaluation of health care programmes, 3rd ed. Oxford University Press, Oxford
Drummmond M, Manca A, Schulpher M (2005) Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. Int J Technol Assess Health Care 21:165–171
Drummmond MF, Wilson DA, Kanavos P, Ubel P, Rivara J (2007) Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care 23:36–42
Eng CM, Guffon N, Wilcox WR et al (2001) Safety and efficacy of recombinant human alpha-galactosidase A: replacement therapy in Fabry’s disease. N Engl J Med 345:9–16
