A Cost-Effectiveness Analysis of the Orphan Drug Cysteamine in the Treatment of Infantile Cystinosis

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Objective. Cysteamine is a recently licensed orphan drug used to treat the inherited metabolic disease cystinosis. The drug delays the onset of renal failure in cystinotic patients and may provide many other significant health benefits. This study examined the cost-effectiveness of the administration of cysteamine to cystinotic patients prior to end-stage renal disease (ESRD). Method. Decision-tree analysis and cost-effectiveness analysis. Cost data were estimated from current clinical charges and Medicare public-access reports. Life expectancy outcomes were derived from both published and unpublished clinical studies and from the U.S. Renal Data System. Results. Cysteamine therapy can extend the life of kidneys and delay renal transplantation, thereby increasing life expectancy for patients with cystinosis. Patients receiving cysteamine therapy prior to renal failure have lifetime-treatment drug costs of $234,000, in comparison with $238,000 for those who are not medicated. Costs of cysteamine therapy are offset by savings associated with delaying transplantation and costs of dialysis. Conclusions. Use of the orphan drug cysteamine both improves health outcomes and reduces health care costs for patients with cystinosis. Key words: cystinosis; cysteamine; decision analysis; cost-effectiveness. (Med Decis Making 1997;17:193-198)

Cystinosis is an autosomal recessive metabolic disorder in which the amino acid cystine accumulates within tissues because of a defect in lysosomal cystine transport. The kidneys are the first organ affected, and patients with the most common type of cystinosis develop symptoms of generalized renal tubular dysfunction by 6-18 months of age. Although the tubular dysfunction is usually easy to treat, these children grow poorly, and their glomerular function deteriorates, leading to end-stage renal failure before 10 years of age. Before the advent of renal transplantation, the only other organ known to be involved was the thyroid. By 10 years of age, half of the patients required thyroxin-replacement therapy. With renal transplantation, many of these patients have survived, and several are now in the fourth decade of life. As these patients have survived to adulthood, many other tissues and organ systems have become damaged, including the eyes, pancreas, central nervous system, and muscle. Many patients have become blind, died during stroke-like episodes, or developed severe myopathy. Some patients have died after choking on food because of severe weakness of the swallowing mechanism. The gene responsible for this condition has been mapped to the short arm of chromosome 17, but it has not yet been cloned. It is likely that there are many sites of abnormality in this gene, which would account for the differing clinical types of the disease. In 1976, Thoene et al. reported that cysteamine rapidly depletes cystinotic cells of their abnormal stores of cystine, and clinical trials began shortly thereafter. It is now known that the cysteamine enters the lysosome where the abnormal cystine stores reside and forms a mixed disulfide with cystine that is able to rapidly exit the lysosome via the cationic transport system, which is intact in these patients.

Cysteamine's use in cystinosis was difficult to study, for several reasons. The drug has a very nauseating smell and taste, which makes it impossible to do masked studies and leads to very poor patient compliance. This was especially true before families realized how helpful the drug was for cystinotic children. Nonetheless, in 1976, Gaul et al. reported the...
efficacy of this drug in supporting glomerular function in cystinotic children.\textsuperscript{23} and, since this publication, cysteamine has been the drug of choice for these children.\textsuperscript{1, 24} Although it is not proven that cysteamine will prevent damage to other organs in cystinotic patients, it is known that this drug will prevent the accumulation of cystine in both muscle and liver, and it is reasonable to expect that it will prevent damage to other organs.\textsuperscript{25}

Early studies of cysteamine were supported by funds from the National Foundation/March of Dimes, and the National Institutes of Health, and gifts from the Pharmaceutical Manufacturers Association and the Generic Pharmaceutical Industry Association Institute for Orphan Drugs. After the 1987 New England Journal of Medicine publication, it become increasingly difficult to obtain outside funding to pay for this drug, since funding agencies rightfully pointed out that the studies were already done and this drug was already the drug of choice for children with cystinosis. The FDA acknowledged this in 1991, when they gave us (JAS) specific permission to charge for the exact cost of providing cysteamine to children with cystinosis. Nonetheless, many insurance companies refused to pay for the drug, since their contracts generally said that they would reimburse only for drugs that were officially approved by the FDA. The FDA could not approve the drug until it was proposed for New Drug Approval, and it was extremely difficult to find a pharmaceutical company willing to do this for a drug that would have a maximum patient base of only 300–400 in the United States. In seeking payment from insurance companies, we pointed out that the drug would improve the caliber of life of these patients by maintaining renal function and also by preventing damage to non-renal organs. Furthermore, there would be a cost savings because the need for renal dialysis and/or renal transplantation might be prevented. Insurance companies did not seem impressed by these arguments, and because of this, we attempted a cost-effectiveness analysis of the use of this drug in children with infantile cystinosis.

\textbf{Method}

We used cost-effectiveness analysis to evaluate cysteamine treatment for patients with cystinosis. The analysis used a societal perspective to evaluate costs because the costs of renal failure accrue to Medicare and the end-stage renal disease (ESRD) program. Although Medicare does not pay for cysteamine for patients who have not reached ESRD, investment in ESRD prevention may save money for the program. The major data sources were published articles and national Medicare cost data from the ESRD program. A formal decision analysis was performed for the most conservative treatment outcome in which the parameters were life expectancy and expected lifetime treatment costs.

\textbf{ASSUMPTIONS}

The base case assumed a pediatric cystinosis patient in whom renal failure would be delayed for five years with cysteamine. The clinical strategies involved either administration of cysteamine until onset of first renal failure or no treatment prior to renal failure. After renal failure all patients were assumed to follow a potential course of dialysis, first transplant, graft failure, second dialysis, second transplant, graft failure, and maintenance dialysis to death. Third transplants were not included because of their relative scarcity.\textsuperscript{26, 27}

The recommended daily dose of cysteamine (as Cystagon\textsuperscript{TM}) is 1.3 g/m\textsuperscript{2}/day. This dose is given in four divided doses as close to every six hours as possible. The dose is monitored by measuring the leukocyte cystine content every three to four months. When blood is obtained for leukocyte preparation five to six hours after a dose of cysteamine, the cystine content should be less than 1.0 nmol half-cystine per mg protein for optimal benefit. The level of compliance with cysteamine therapy is unknown. In a previous study with cysteamine hydrochloride, 14% of patients found this drug so foul-tasting and odorous that they stopped taking it.\textsuperscript{28} Cystagon is encapsulated and not likely to have the high rate of noncompliance seen with cysteamine hydrochloride. However, this form of cysteamine has been used for too short a time to be certain.

Decision-tree analysis incorporated the probabilities of various outcomes, including death on dialysis while awaiting transplant, operative transplant mortality, and successful transplant. Other relevant data included mean time to first renal failure, life expectancy on maintenance dialysis, and graft survival post-transplant.

\textbf{ESTIMATE OF COST}

Cost data for drug treatment were derived from current charges at the University of California, San Diego, for medication and measurement of leukocyte cystine content. Medicare reimbursement was used to estimate the costs of routine blood chemistry panels and physician follow-up visits. All ESRD treatment costs were derived from the Medicare ESRD cost figures.\textsuperscript{27, 28} A discount rate of 5% per year was used in calculating future costs. This has been viewed as a conservative estimate in the range of acceptable values.\textsuperscript{29}

We originally (in 1992) prepared a life-table analysis of the cystinosis patients who had been receiving cysteamine and compared it with a similar anal-
ysis done ten years earlier in cystinosis patients who had never received this drug. The 1992 analysis of cysteamine-treated patients revealed a median renal survival time of 15 years, an increase of five years compared with those who had not received the drug. In 1993, an analysis of all of the cystinosis patients treated with cysteamine at the National Institutes of Health suggested that patients who started the drug before 2 years of age, and were compliant in taking the drug, as estimated by maintaining their leukocyte cystine content below 2 nmol half-cystine per mg protein, would have normal life expectancies.

ESTIMATE OF HEALTH EFFECT

In order to calculate mean time to first renal failure, life tables were analyzed. Life tables for children with cystinosis were created using data from a European collaborative study. The effect of treatment was estimated from the time of 50% renal survival. Life-table analysis of cysteamine-treated patients revealed a 50% renal survival time of 15 years. Cystinotics not treated with cysteamine had a 50% renal survival time of nine and one-half years. Operative mortality of pediatric renal transplantation was obtained from the European Registry.

After renal failure or first graft failure, all patients were assumed to undergo dialysis while awaiting transplant. All ESRD data regarding waiting times to transplant have been adjusted to ratios of living-related donors to cadaver donors in the year 1984. This corresponds to the year of transplant used in approximating the mean survival time. Life-table analyses for graft survival and survival on maintenance dialysis were unavailable because of the limited time period covered by the U.S. Renal Data Systems. Mean survival time on maintenance dialysis and mean graft survival were both approximated for this reason. Tables 1 and 2 show the data used to estimate these figures. These are based on the USRDS age cohort of 25–30-year-old patients entering dialysis. In our model, patients enter maintenance dialysis after two transplants at age 28–32 years. Survival on maintenance dialysis is adjusted for patients’ ages. Low estimates were used in the estimation of mean survival time under these treatments. All data used in the decision-tree analysis are listed in tables 3 and 4 with their corresponding sources.

Table 1 • Life-table Data for Graft Survival Approximation*

<table>
<thead>
<tr>
<th>Living–Related Donor (n = 95)</th>
<th>Cadaver Donor (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>% Survival</td>
</tr>
<tr>
<td>1 year</td>
<td>91.58</td>
</tr>
<tr>
<td>2 years</td>
<td>84.21</td>
</tr>
<tr>
<td>3 years</td>
<td>77.90</td>
</tr>
<tr>
<td>5 years</td>
<td>68.41</td>
</tr>
</tbody>
</table>


Table 2 • Life-table Data for Maintenance Dialysis Survival Approximation—Beginning 1977*

<table>
<thead>
<tr>
<th>Age</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>89.38</td>
</tr>
<tr>
<td>2 years</td>
<td>85.05</td>
</tr>
<tr>
<td>5 years</td>
<td>80.02</td>
</tr>
<tr>
<td>10 years</td>
<td>68.91</td>
</tr>
</tbody>
</table>


Cost—Effectiveness of Cysteamine in Cystinosis

Table 3 • Costs of Relevant Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-stage renal disease treatments*</td>
<td>$56,000</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>$56,000/year</td>
</tr>
<tr>
<td>Transplant maintenance</td>
<td>$6,000/year</td>
</tr>
<tr>
<td>Maintenance dialysis</td>
<td>$32,000/year</td>
</tr>
<tr>
<td>Cysteamine treatment</td>
<td>$1,600/year</td>
</tr>
<tr>
<td>Medication</td>
<td>$1,200/year</td>
</tr>
<tr>
<td>3 WBC cystine measurements/year</td>
<td>$225/year</td>
</tr>
<tr>
<td>3 outpatient visits/year</td>
<td>$384/year</td>
</tr>
</tbody>
</table>

*From Levinsky and Rettig.

Table 4 • Life Expectancies of Patients with End-stage Renal Disease with Relevant Treatments*

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to renal failure without medication*</td>
<td>10 years</td>
</tr>
<tr>
<td>Time to renal failure with medication*</td>
<td>&gt;15 years</td>
</tr>
<tr>
<td>Waiting period for transplant*</td>
<td>1 year</td>
</tr>
<tr>
<td>Percent mortality awaiting transplant*</td>
<td>10%</td>
</tr>
<tr>
<td>Percent mortality of transplant operation</td>
<td>5%</td>
</tr>
<tr>
<td>Time to graft failure with renal transplant</td>
<td>7 years</td>
</tr>
<tr>
<td>Time to death on maintenance dialysis*</td>
<td>15 years</td>
</tr>
</tbody>
</table>

*For complete reference information, see the reference list.

Results

DECISION-TREE ANALYSIS

The decision-tree analysis was programmed on the DATATree program to calculate cost and life expectancy over the lifetimes of patients. Figure 1 graphically represents the decision tree generated for this study. The first decision point divides those patients who are treated with cysteamine upon diagnosis of cystinosis and those that are allowed to remain untreated. Subsequently, both sets of patients are assumed to follow similar courses, as described in the methods section. The only significant difference between the two populations is the time before first renal failure.
COST ANALYSIS

Using an estimate of five additional years before renal death, patients receiving cysteamine therapy prior to renal failure have lifetime treatment costs of $234,000 and nonmedicated patients have lifetime treatment costs of approximately $238,000. Cysteamine therapy prior to renal failure reduces lifetime treatment costs of patients with cystinosis by $4,000. The costs of cysteamine therapy are offset by the cost savings from delaying costly procedures such as transplantation and dialysis.

SENSITIVITY ANALYSIS

The eventual cost of cysteamine in commercial production is unknown. For this reason, sensitivity analysis was used to determine the maximal drug cost before the lifetime treatment costs of the medicated cystinotic patients exceeded that of the non-medicated patients.

Low estimates were used for the effects of cysteamine treatment, mean graft survival time, and mean life expectancy on maintenance dialysis. Sensitivity analysis was conducted using a higher estimate of ten years for delay of time to first renal failure. Sensitivity analysis considered delays in the onset of renal failure of one through four years. The expected treatment cost for a five-year delay ($234,000 in the base case) increases to $241,000 with a four-year delay, $247,000 with a three-year delay, $254,000 with a two-year delay, and $263,000 with a one-year delay. The maximal drug cost was calculated under these conditions, looking for the point where lifetime treatment costs of medicated patients began to exceed those of non-medicated patients.

COST–EFFECTIVENESS ANALYSIS

Life expectancy increases by at least five years per patient due to the delay of time to first renal failure. Nonetheless, total program cost decreases. Cysteamine treatment of cystinosis maximizes cost–effectiveness by both decreasing program costs and improving treatment outcomes.

In the case of a five-year delay in the onset of renal failure, sensitivity analysis revealed a maximal drug cost of $3,000/year before lifetime treatment costs outweighed the treatment costs without cysteamine. This represents an 18% increase over the current charges. With a ten-year delay in the onset of renal failure, a much larger savings in lifetime treatment costs results. Under these circumstances, drug costs could increase 238% over current levels before lifetime treatment costs with medication exceeded those of treatment without medication.
Discussion

Cysteamine has been shown to delay the onset of renal failure in cystinotic patients by at least five years.\textsuperscript{24,25} However, cysteamine was not widely available until its approval by the FDA in August 1994. This had led to continuing difficulty in obtaining reimbursement for cysteamine treatment. Decision analysis has shown that even under conditions that probably underestimate the drug's effectiveness, lifetime treatment costs of cystinotic patients can be decreased by using cysteamine. The cost-effectiveness of cystinosis treatment is increased with cysteamine due to these lower costs and improved outcomes. Analysts often evaluate cost-effectiveness in a two-dimensional (cost by outcome) matrix. Some options improve health outcome but increase cost. Others show the health consequences of reducing cost. These two cells in the matrix are often considered in relation to other options. However, there are two other cells in the matrix for which the decision is straightforward. These include treatments that both increase cost and reduce health (and should be rejected) and those that decrease cost and improve health (which should always be endorsed). The treatment of cystinosis with cysteamine falls within this latter, clear-decision, category.

The calculations used in this analysis were conducted with data judged to be the least refutable given current knowledge. Many patients who have undergone treatment with cysteamine for over ten years show no sign of progressing towards renal failure.\textsuperscript{24} Markello and colleagues argue that cystinosis patients who begin cysteamine treatment before 2 years of age, and who faithfully take the drug as shown by maintenance of the leukocyte cystine content below 2 nmol half-cystine per mg protein, will never need dialysis or transplantation.\textsuperscript{24}

One shortcoming of the present analysis is that outcome is defined only in terms of life expectancy. Clearly, cystinosis affects quality in addition to quantity of life. Unfortunately, data on quality-of-life outcomes are not now available, and it is not possible to provide dependable estimates of quality-adjusted life years (QALYs).\textsuperscript{25} However, it is likely that cysteamine improves quality of life as well as longevity. Thus, life expectancy may offer a more conservative estimate of treatment effect than QALYs. For example, these calculations did not include the likely effect of cysteamine on other symptoms experienced by cystinotics.\textsuperscript{25,26} It has already been shown that cysteamine increases growth velocity and net growth.\textsuperscript{25} Since cysteamine treatment decreases the accumulation of cystine in muscles of cystinosis patients, it is also likely that this drug will prevent the severe myopathy that has occurred in some older cystinosis patients.\textsuperscript{15,16,20} It is possible that cysteamine will also prevent the central nervous system abnormalities that have been reported to occur in some older cystinosis patients.\textsuperscript{4,11–16}

These additional health benefits support the use of cysteamine after renal transplantation. The added lifetime treatment costs would be $27,523 using the low estimates of efficacy and $17,256 for the higher estimates of drug efficacy in delaying renal failure. When considering additional lifetime treatment costs using the low estimates of efficacy, the improvements in quality of life must be considered, given that the total lifetime treatment cost for a medicated patient exceeds that for a non-medicated patient by $12,433. However, in the likely case that these values underestimate drug efficacy, the added costs do not change the results of the cost-effectiveness analysis. Using our higher estimates of delay to onset of renal failure, lifetime treatment costs of medicated patients remain $11,130 less than those of non-medicated patients even when the cost of cysteamine over their entire lifetimes is included.

The cost savings with cysteamine treatment result from delaying expensive ESRD treatments such as dialysis and transplantation. These treatments are covered by the Medicare ESRD program, and the net savings are to the federal government. This is because the Medicare program assumes responsibility of payment for the care of patients with end-stage renal disease. However, payment for drug treatment to cystinotics prior to renal failure often falls to private insurers. Many private insurers have been reluctant to reimburse for new or rare drugs. It now appears clear that current data can be used to justify reimbursement for cysteamine treatment. While insurance companies pay more in the short run, the government will see much larger savings over the lifetime treatment of cystinotics. Furthermore, patients will benefit from improved outcomes.

Jerry A. Schneider served as a consultant to Mylan Pharmaceuticals while they developed the New Drug Application for Cystagon.\textsuperscript{4} He currently has support from Mylan to develop a “databank” that will allow him to follow all cystinosis patients in the United States who receive cysteamine. Mylan provided no support for the research reported here.

References