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### Dry powder inhalation of biopharmaceuticals

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# CHAPTER 6

## Pharmaco-economic Review of Recombinant Human DNase (rhDNase) in the management of Cystic Fibrosis; with special reference to current developments in delivery systems

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## ABSTRACT

For treatment of patients with cystic fibrosis, recombinant human deoxyribonuclease I (rhDNase) is widely used. RhDNase has a positive effect on the lung function and on the number of hospitalizations. RhDNase is currently administered by nebulization, which is an inefficient administration method. For expensive drugs, such as rhDNase, dry powder inhalation would be advantageous due to increased deposition efficiency, patient mobility and patient compliance. Furthermore, a significant cost reduction might be obtained. We therefore investigated the current status of rhDNase in the management of cystic fibrosis and gave special attention to developments in delivery systems as dry powder inhalation. We preliminarily estimated that if dry powder inhalation of rhDNase could be used, a reduction in the cost-effectiveness ratio of almost 40% can be obtained as compared to nebulization.

## INTRODUCTION

Recombinant human DNase (rhDNase) is a mucolytic agent, which reduces the viscoelasticity of sputum and is therefore a possible therapy in cystic fibrosis (CF) patients. RhDNase is currently administered by means of nebulization. However, nebulization is a rather inefficient delivery method. Improved administration of rhDNase would in several aspects be advantageous for CF patients.

Dry powder inhalation (DPI) of rhDNase seems to be a promising example of a more efficient delivery method of rhDNase in CF patients. Because of the high costs of rhDNase, DPI of rhDNase could be cost-saving, compared to the nebulization of rhDNase.

In this review, we evaluate the pharmacoeconomical aspects in the management of rhDNase of CF. Developments in nebulization and DPI delivery systems of rhDNase are compared. Furthermore, aspects with respect to efficacy, tolerability, safety and compliance of rhDNase (nebulization vs. DPI) are outlined.

After weighting the advantages and disadvantages of rhDNase and the delivery systems, an expert opinion and a five-year view with respect to the rhDNase delivery in patients with CF, are described.

## CYSTIC FIBROSIS AND RECOMBINANT HUMAN DNASE (RHDNASE)

### Epidemiology and Pathophysiology

CF is the most frequently observed genetic disorder in the white population with a potential lethal outcome. CF affects approximately 1 in every 2500-3400 live births and 3.3% is carrier of the defective gene among Caucasians (1-3).

The disease is autosomal recessive, meaning that the gene relating to this disease is not present at the sex chromosome (autosomal) and that a person can carry a defect gene and not have the symptoms but can pass it on to the next generation (recessive). In the Netherlands about 1000 patients have CF, while 1 in every 30 persons carries the defect gene (4). The defective gene is located on chromosome 7. Approximately 70% of the CF cases are caused by a 3 base-pair deletion ( $\Delta F508$ ). The remaining CF cases are arising from about 600 different mutations of the gene (3, 5).

CF is a chronic disease that varies in the underlying systems involved and the severity of the symptoms. This is partly due to the genetic mutations, but also to environmental and treatment factors. In patients with CF

much variability is therefore seen and assessment of the efficacy and effectiveness of treatment strategies takes a long time because of uncertain progression (6).

Complications of CF include pulmonary symptoms, pancreatic insufficiency (in 85% of the patients) leading to malabsorption of fat and malnutrition, diabetes mellitus, biliary cirrhosis, subacute bowel obstructions, arthritis and infertility. Although prevalence is relatively low, the treatment burden per patient may be quite high and can lead to chronic disability at any age (7-9).

Over 85% of the CF patients die from progression of their lung disease (5, 10). Individuals with CF have a mean life span of about 30 years (8). Dietary strategies and new treatments of pulmonary symptoms have led to an increase in average survival of CF patients from only 6 years in the 1960s to about 30 years in the 1990s (11-14). The quality of life for CF patients have also improved dramatically the last decades, due to regular periodic evaluations, monitoring for complications of the disease, and new interventions by physicians and other healthcare workers specifically trained in management of CF (11, 15).

Respiratory Tract Infections (RTIs) are a major cause of hospitalization of CF patients. More than one-third of the CF patients are hospitalized each year, and 20% of the CF patients are hospitalized more than twice a year. Of all CF-related hospitalizations, more than 75% is for treatment of RTIs (16, 17).

The high number of RTIs is a direct consequence of the genetic defect underlying CF. A mutation in the cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP-dependent chloride channel, causes a defect in the transmembrane chloride transport. This leads to diminished transluminal chloride transport, which results in a relative dehydration of the luminal surface of the exocrine glands. In the lung, the dehydration causes a viscid mucus layer which inhibits a normal ciliary clearing and thus facilitates bacterial colonization of the respiratory tract. Bacterial colonization, most commonly with *Staphylococcus aureus*, *Haemophilus influenza* and *Pseudomonas aeruginosa*, accounts for much of the morbidity and virtually all mortality in CF patients by means of RTIs (1, 2, 7, 8, 16, 18, 19).

After chronic pulmonary infection the viscoelastic properties of purulent airway secretions are primarily caused by DNA from degenerating neutrophils. The presence of DNA increases the viscosity of sputum and

makes it more difficult to clear the sputum from the respiratory tract. This increases the susceptibility to infection which, in turn, provokes an inflammatory response. Therefore, a cycle of infection, inflammation and obstruction leads to progressive destruction of lung tissue and reduced life expectancy (20, 21).

The pulmonary inflammation in patients with CF begins in infancy, is present in babies of about 4 weeks (8), and is probably established when the child is 1 year old (22). The lower respiratory tract of 40% of the children with CF younger than 3 months, has been found to be colonised and in these, as well as in older children, airway DNA levels are also increased (8, 23). This suggests that early inflammation can cause lung injuries, which results in higher susceptibility for inflammation (8).

### Pharmacology and Therapy

Patients with CF undergo complex, multidrug treatment aimed on treating the various symptoms of the disease. Alleviating the effects of chronic inflammation and infection in the airways is one of the major objectives. In the last 30 years, airway obstruction reducing agents, airway infection controlling agents, and agents that improve the nutritional status have become the cornerstone of successful treatment in patients with CF (8, 24). Next to these strategies aggressive symptomatic treatment of complications of the lung disease is also important. New treatment strategies are focussed on repair of the basic gene-defect and include manipulation of the ion-transport, activation of mutant CFTR and gene therapy (24, 25).

An important aspect of CF-therapy is the use of mucolytic agents. An example is deoxyribonuclease, which hydrolyzes extracellular DNA and therewith reduces the viscoelasticity of sputum in patients with CF (26). In 1958, bovine pancreatic DNase I was approved in the United States for human use (Dornavac or Dornase). DNase showed a large reduction in viscosity *in vitro* and in one study it was suggested that bovine pancreatic DNase I was reasonably safe and effective in reducing the viscosity of lung secretions (27).

However, for bovine pancreatic DNase I it has been reported that adverse reactions (possibly due to contaminating proteases in the final product) occurred after inhalation, causing the non-human protein to be no longer used (27, 28).

In 1990, recombinant human DNase I (rhDNase) was cloned, sequenced and expressed. RhDNase was *in vitro* shown to dramatically reduce the viscosity of the sputum of cystic fibrosis patients, transforming it within minutes from a viscous non-flowing gel to a flowing liquid (21, 27). Part of the action of rhDNase is explained by cleavage of highly polymerized DNA. Decreasing the chain length of DNA by rhDNase results in a lower viscosity (21). An *in vitro* study showed that the phospholipid concentration (phosphatidylglycerol, dipalmitoylphosphatidylcholine) is increased when the mucus is in its sol phase. The phospholipids are being liberated by rhDNase and then lubricate the mucus, thereby improving the effect of cough and ciliary clearance (28).

In this review, we will focus on the therapy of recombinant human DNase (rhDNase) with special reference to development of delivery systems. Special attention is given to the rational development of RhDNase as a pharmaco-economically effective drug. In the next section it is motivated that the delivery of rhDNase as a dry powder for inhalation would have enormous pharmaceutical and economical advantages over the current nebulization.

### Delivery systems of rhDNase

In order to achieve high local and low systemic concentrations, inhalation is the most advantageous route of administration. Alternative routes of delivery would be very inefficient due to the poor permeation of rhDNase (~ 34 kDa) to airway lumen from the vascular system.

Up to now, rhDNase is administered by means of nebulization. However, maintenance treatment of CF patients with nebulized rhDNase immobilizes the patient to a great extent: there is need for a compressor unit or pressurized air for the jet nebulizer or electricity if an ultrasonic nebulizer is used. Furthermore, the low efficiency is a major drawback. It has been reported that for the jet nebulizers, the type recommended for rhDNase, the efficiency (i.e. the percentage of drug that is available for therapeutic action after the inhalation manoeuvre) is only 2-12% (29). Although rhDNase delivered by nebulization is effective on the short (i.e. 10 days (30, 31)), medium (i.e. 6 weeks (1), 12 weeks (2) and 6 months (32, 33)) and long term (2 years) (34, 35), improved administration would be advantageous for the patient and may have economic benefits. With dry powder inhalation (DPI) there is no need for pressurized air or electricity: the patient delivers the driving force for administering a dose

by means of an inhalation manoeuvre (29, 36). Moreover, DPI has the potential for a more efficient (deep) lung deposition, reports describing efficiency of up to 60% have appeared (37, 38) and new technologies are currently developed (39, 40). A switch from nebulization to DPI is therefore likely to increase patient compliance (dosing time, patient mobility) and therapeutic efficacy (29, 36).

Although the development of a DPI-formulation of proteins is more complex, it is possible to develop such a formulation (41-44). In this review, we examined the consequences of the choice of type of formulation (nebulization vs. DPI) on healthcare costs.

### Cost of illness

In the last decennia, new treatment strategies of CF increased median survival of this disease by a factor 5 (8). Cost estimates from developed countries indicate CF as a very expensive disease. Estimates of the annual cost per CF patient vary between €1,954 and €13,969 (45). For the Dutch situation the costs of CF were estimated to account for 0.07% of the health care budget (46). Life time costs for CF patients, assuming the life expectancy to be 25 years have been estimated to be approximately €225,000 (8). In another study, costs of care in patients with CF to the age of 35 were estimated to be €430,211 (47).

Costs of a disease are divided in direct and indirect costs. For CF the clinical visit, hospital admission, outpatient drug costs (for example; rhDNase, antibiotics and dispensing fees) and laboratory tests are seen as direct costs. Direct non-medical costs include out-of-pocket expenses for dietary recommendations and travel costs to receive care. The indirect costs include for example productivity losses (48). These indirect costs were often disregarded in the reviewed publications on CF costs.

Direct costs, such as costs for medication, account for most expenses of medical care in CF patients. Total costs were estimated to be around €5,250 per patient per year (49). Due to interindividual differences not all patients benefit from rhDNase (24, 48-51). The differences in costs depend on changes in respiratory function and possibility of exacerbations. The Dutch costs of rhDNase were estimated to be about 2,5 million Euro's in 1997 and were estimated to remain constant the following years (52).



Next to medication, rates of exacerbations of CF and symptoms of this disease and hospitalization are the largest cost components. More than 1 out of 3 patients with CF are hospitalized each year (16, 53). Over 3 out of 4 patients admitted are treated for pulmonary infections. The costs per admission were estimated to range from €7,840 to €28,000 (16, 53, 54). Different studies estimated the percentages of different cost-components for direct costs in CF. Table 1 shows these results

Table 1. Direct costs of CF: percentage of distribution

Reference:	(48)	(45)	(47)	(55)
Hospital care	33%	-	42%	47%
RhDNase	44%	-	-	18%
Clinic visits	12%	-	-	12%
Laboratory tests	8%	-	-	-
Medication (other than rhDNase)	3%	57%	37%	10%
Other	-	43%	21%	13%

As can be seen in table 1, medication costs and hospital care are the largest component of the costs. RhDNase offers a therapeutic opportunity to reduce RTI-related health care use in CF patients. The objective behind therapy with rhDNase is improving health related quality of life and additionally lowering the costs of CF. As described above, several cost components (hospitalization, exacerbations, symptoms, therapy, RTI-related, antibiotics, etc) have to be taken into account when estimating the cost-benefit ratio of rhDNase therapy in CF patients. RhDNase contributes significantly to the costs of treatment of CF (56). Therefore, if these costs can be reduced by development of a dry powder formulation for inhalation, significant benefits may be gained.

### Quality of Life considerations

The respiratory symptoms of CF can adversely affect daily activities of the patient with CF, because of the unpredictability of these symptoms and serious consequences of exacerbations. It is difficult to predict the degree to which the quality of life of an individual can be affected by CF. Some studies mention that the great majority of CF patients live well in adulthood with an acceptable quality of life, due to basic therapies. New therapies can help to improve the quality of life (9, 57). However, all

patients suffer from deterioration in their disease, which leads to limitations and thus ultimately reduces quality of life significantly (9).

The majority of morbidity and mortality in CF results from inflammation and infection of the airway lumen, which leads to a certain degree of disability in patients with CF (58). In one study, the impact of pulmonary exacerbations on quality of life in CF patients was studied (59). The objective was to compare health-related quality of life (HRQOL) of CF patients to general population and to determine the relationship between HRQOL and clinical and demographic factors.

For measurement of HRQOL, five aspects of health were included: physical functioning, role functioning, mental health, social functioning and general health perceptions. HRQOL measures the individual ability to function in each area and the individuals evaluation of their functioning (59).

The study of Britt et al. [56], showed that exacerbations do not have a profound negative impact on HRQOL that is not explained by differences in function of lungs, nutrition status or demographic factors. In spite of this, lung function, nutrition, 6-min walk, age, gender, and insurance status were not significantly associated with HRQOL in this study population (59).

On short term, well-being and quality of life of CF patients is improved by rhDNase, through improvement in lung function and a reduction of RTI-incidence (14, 50).

In the study of Oster et al. (16), questionnaires were developed to evaluate well-being (feeling, energy, activity, sleep, appetite) and physical symptoms (sputum production, frequency and severity of cough, chest congestion). The results mentioned that compared to the placebo-group, there was significantly less dyspnoea, significantly improved well-being and there were significantly fewer CF related symptoms in the rhDNase-group. This implies that when CF patients are treated with rhDNase they have a better quality of life compared to patients who are not treated with rhDNase.

Another study noted that baseline HRQOL assessments show that adults with CF, reported decrements in health status and functioning. In this study, a significant association was found between the rhDNase therapy and one-year change in HRQOL. One of their suggestions was that a further evaluation of the relation between hospital admission and changes in HRQOL is required (17).

As opposed to life expectancy, morbidity and mortality, quality of life is mainly not affected by the CF disease as such (e.g. dietary requirements), but much more by the symptoms and respiratory tract inflammations and infections. Hospitalization affects quality of life also in a negative sense. RhDNase has a positive short-term effect on the quality of life as mentioned above. In the reviewed studies, long-term effects and delivery of rhDNase were not evaluated with respect to quality of life in patients with CF.

## METHODS

We searched for articles on recombinant human DNase (rhDNase) in international literature databases (Medline and Embase), which were published in English and Dutch in the beginning of the nineties. Additional references were identified from the reference lists of these articles.

The search terms were 'cystic fibrosis', 'recombinant human DNase (rhDNase)', 'dornase alpha', 'pharmaco-economics', 'cost-effectiveness', 'cost-utility', 'health- economics', 'dry powder inhalation', 'aerosol inhalation', 'nebulization' and 'delivery (systems)', or one of the possible combinations of these terms. The searches were last updated February 18<sup>th</sup>, 2003.

The selection was based on articles with economic analyses in patients with cystic fibrosis that receive rhDNase by inhalation. All pharmacoeconomic analyses, such as cost-effectiveness, cost-utility and cost-benefit analyses, were included. Articles on efficacy, tolerability, safety and compliance with respect to rhDNase, were also included in this review. Papers on efficacy, tolerability, safety and compliance are reviewed in the next section, as these provide the basis of pharmacoeconomic assessments. Section 5 reviews the general pharmacoeconomics, whereas section 6 considers the drug-delivery systems with regard to economics.

## CLINICAL PROFILE OF INHALED RHDNASE

### Efficacy

The Cystic Fibrosis Foundation has suggested a definition of the disease severity based on the Forced Expiratory Volume in 1 second (FEV<sub>1</sub>) and the corresponding Forced Vital Capacity (FVC):

- Mild: FEV<sub>1</sub> ≥70% of predicted value or FVC ≥85% of predicted

- Moderate:  $40\% \leq FEV_1 < 70\%$  of predicted value or  $60\% \leq FVC < 85\%$  of predicted
- Severe:  $FEV_1 < 40\%$  of predicted value or  $FVC \leq 60\%$  of predicted (8).

Most of the reviewed studies used a daily dose of 2.5 mg rhDNase in patients with CF and observed the short term effects of rhDNase. Long-term effects (benefits) are not yet available. Consequently, it is uncertain to what extent the short-term effects can be used to predict any long-term benefit (60).

Fuchs et al (54) found a reduction in exacerbations of respiratory symptoms and a slight improvement in pulmonary function after 2.5mg rhDNase therapy in a randomized, double-blind, placebo-controlled study in which 968 patients participated. One or more exacerbations occurred in 27% of the patients who received a placebo, 22% in patients who received once daily rhDNase and 19% in patients who received twice daily rhDNase (2 x 2.5 mg). The  $FEV_1$  improved with about 6% in patients who received rhDNase (24, 53, 54). The study of Menzin et al (6) showed that the reduction of the viscosity of purulent sputum by rhDNase as is studied in early clinical trials of aerosol delivery, accomplishes improvement in pulmonary function ( $FEV_1$ ) of 10 to 15% in patients with CF. In this study, a reduction in RTIs as consequence of rhDNase therapy was also found.

Cobos et al (61) studied the minor to moderate benefits in short-term clinical trials. In this study, 166 patients continued rhDNase therapy during the data collection. After one and after two years of treatment with rhDNase, the mean changes in  $FEV_1$  were 3,3% and 5,1%, respectively. At the end of the same periods 34% of patients had improved their baseline  $FEV_1$  by 10% or more but in about 50% of the patients the level fell below the baseline. The medium-term response to rhDNase treatment was correlated with an early response during the first 3 months. There was a large inter-individual difference in change in pulmonary function documented and there were no consistent changes in exacerbation pattern found during the first year of rhDNase treatment.

Johnson et al (48) performed an observational study in 283 CF patients (>6 years;  $FEV_1 < 40\%$  predicted). The treatment group received 18 months rhDNase, while the control-group, consisting of 2382 patients, had never received rhDNase. The  $FEV_1$  for patients treated with rhDNase improved with 3,9% of the predicted value while the untreated control group had a decline in  $FEV_1$  of 1,6% of the predicted value. This study

provided some evidence for effectiveness, without statistical significance, of rhDNase.

Milla (35) studied patients with CF retrospectively on spirometric parameters for two years. 190 Patients were included, who after two years of rhDNase administration showed a positive trend with respect to malnutrition and hardly hospital admissions. There was a mild decline in FEV<sub>1</sub>, while FeV<sub>1</sub>/FVC remained stable.

In the study of Geller (23) characteristics of two different aerosol delivery systems that might affect efficacy in patients with mild CF, were reviewed. The reviewed systems were a Hudson T Up-draft II with a Pulmo-Aide compressor or the Durable Sidestream nebulizer, powered by a CR50 compressor. The delivery system with the smaller droplet size - the Sidestream nebulizer - tended to provide more improvement than the system with a larger droplet size. The results of the study indicate a statistically not-significant improvement in CF patients who received the smaller particle size aerosol (4.3% versus 2.5%,  $p = 0.06$ ).

Johnson et al (7) showed in a phase III trial that rhDNase therapy (once or twice daily; 24 weeks) in CF patients resulted in significant reductions in the number of respiratory symptoms and exacerbations in lung disease. This resulted in a reduction in the use of parenteral antibiotics and significant improvement in pulmonary function and also a reduction of hospitalizations.

Suri et al (12) compared the consequences of three therapies in children: 1) daily rhDNase (2.5 mg), 2) alternate day rhDNase (2.5 mg) and 3) hypertonic saline (two times per day) during 12 weeks. The study was an open randomised cross-over trial, in which 48 children with CF were allocated. This resulted in a significant greater increase in mean FEV<sub>1</sub> (2-14%) with daily rhDNase compared with hypertonic saline, while daily and alternate daily rhDNase did not differ significantly.

In another clinical trial, Grieve et al (51) investigated the effect of 12 weeks treatment with daily rhDNase, alternate day rhDNase or hypertonic saline (HS) in a randomized, crossover study, in which 40 children with CF were allocated. They found a 14% (5-23%) improvement in FEV<sub>1</sub> for daily rhDNase compared with HS, while alternate day rhDNase compared to HS resulted in a 12% (2-22%) improvement in FEV<sub>1</sub>. There was, as also described by Suri et al (12), little difference between FEV<sub>1</sub> of daily and alternate day rhDNase.

The publication of Conway (50) provides evidence that rhDNase is effective in patients older than 5 years of age. Early studies of rhDNase showed an increase in baseline FEV<sub>1</sub> of about 9-14% and that the improvement in pulmonary function maintained at a plateau about 6% higher than placebo for continued rhDNase treatment. A similar effect is seen for FVC. Also it was mentioned that a 24 week phase III study resulted in a decrease of RTIs and exacerbations, which reduced antibiotic therapy by 28 to 37% and also reduced the number of hospitalizations. The longer term effects in 188 patients showed persistent benefit for FVC of 9% of predicted and for FEV<sub>1</sub> of 5% of predicted. In a clinical study of a group of 65 children treated with rhDNase for 6 months an increase of 14% in FeV<sub>1</sub> was shown and in 45 of 59 adults with 15 months treatment, an increase of 15% in FeV<sub>1</sub> was achieved, which was maintained by rhDNase therapy (50).

The Pulmozyme (rhDNase) Early Intervention Trial (PEIT) of Robinson et al (62), showed reduction in the risk of pulmonary exacerbations and thereby a reduction of 34% in parenteral antibiotic therapy. This study also showed an improved forced expiratory flow at 25 to 75% of FVC and improvement in FeV<sub>1</sub> over a 2 year period in CF patients with almost normal lung function. The results of this study, conducted at 49 sites in 12 countries in a randomized trial (placebo-controlled) design, showed benefits from rhDNase in CF patients from early intervention in the course of their lung disease.

In another, this time short term, study of rhDNase of Robinson et al (63), an increase of 7.5% in FeV<sub>1</sub> and 5.4% in FVC from baseline was seen in patients who received rhDNase compared with placebo. The authors were unable to demonstrate improvements in either ciliary or cough clearance with regard to the short term use of rhDNase.

The reports of the efficacy as mentioned above are encouraging, with short-term effects of rhDNase relatively positive as indicated in the reviewed studies. In the mild and moderate state of CF improvement in the pulmonary symptoms (measured in FeV<sub>1</sub>, FVC and number of exacerbations) can be of great influence in the reduction of antibiotic therapy and hospitalization of CF patients. This results in a reduction of costs of care in CF. However, the efficacy in severe pulmonary disease is more uncertain, some studies show improvement, some show no differences and some indicate even slight worsening in the number of exacerbations (8). This might be due to large inter-individual differences

with respect to the efficacy of rhDNase. The limited amount of information about the long term effects is a problem in predicting or defining the efficacy of rhDNase.

#### **Tolerability, Safety and Compliance**

Adverse drug events during rhDNase therapy are generally mild and the drug is well tolerated. The most common adverse effects are respiratory related (24). In infants and young children, exposure to rhDNase appeared to be safe over a 2 week period (56).

RhDNase is currently only administered by nebuliser (aerosol). Therefore, it is difficult to find out whether adverse events were related to the drug or to the method of administration. The severity of the disease is of importance in this possible relation. The variability in adherence to rhDNase treatment is a debatable subject in the validation of the safety and efficacy of rhDNase. Nebulization as an administration technique leads to lower compliance to the therapy of CF patients, whilst the compliance is of utmost importance, since the efficacy of the treatment heavily depends on the compliance (64).

Post-marketing clinical experiences have confirmed the relative safety of rhDNase that was documented in clinical trials. Voice alteration, hoarseness, laryngitis, pharyngitis and rash are the most common adverse events in patients using rhDNase (8, 56, 57, 62). These symptoms are self-limited and do not require medication. Next to these adverse events, chest pain and conjunctivitis also have been reported. These events were not more frequently reported than with placebo. The percentage of withdrawal from therapy in the clinical trials was not significantly different for rhDNase compared to placebo (8).

Information on adverse events of rhDNase after long term therapy is scarcely documented. In a two year study in patients with mild to moderate CF, no serious adverse drug events in treatment with rhDNase were found (34).

Up to now, rhDNase has shown to be a well-tolerated drug, which can be used safely with few adverse drug events that do not require new drug therapies to treat those adverse events.

#### **PHARMACO-ECONOMIC ANALYSIS OF AEROSOL RHDNASE**

The few cost(-effectiveness) studies available concerning rhDNase, are often published as abstracts or short reports while fully-reported cost-

effectiveness analyses are lacking. For that reason only little information is available about the methodology and about cost categories. In short, some costing has been done with respect to aerosol rhDNase but a full cost-effectiveness analysis is (yet) lacking (6, 7, 12, 14, 16, 45, 51, 53, 55). Below, the empirical evidence on pharmaco-economics of rhDNase is taken from the four most comprehensive studies on the topic (12, 14, 16, 51). These studies are evaluated with respect to several criteria that we feel are currently the most important for conducting “good” pharmaco-economic research: for example, the societal perspective should be taken (including all relevant cost categories, even indirect costs of production losses if important), taking the adequate time frame (including long-term effects) and results should preferably be expressed per life-year gained (LYG) or per quality-adjusted life-year (QALY) gained (65).

According to Oster et al (16), rhDNase reduced the estimated average costs of RTI-related care over 24 weeks by €912 - €1,884 compared with placebo. Limited to only protocol-defined RTIs, the reduction of the costs was estimated at €681 - €1,057. The findings in this study suggest that rhDNase therapy may prevent approximately 31-33 RTI-related hospitalizations per 100 patients on an annual basis. This would correspond with a saving of €2,016 - €4,144 per patient annually. Also, this paper mentions that the reduced costs of RTI-related care are expected to be about 33% (18.3-37.5%) of the total costs of rhDNase-therapy. As mentioned, this analysis does not include all relevant cost categories that may be specified.

McIntyre (14) used the results of the study of Oster et al (16) to estimate the net costs per LYG as a cost-effectiveness outcome. For that purpose annual costs of rhDNase of €5,040 were assumed. The discounted lifetime costs for a CF patient was estimated at €163,100, including the acquisition costs of rhDNase and the additional costs of treatment for 3 extra years of life. The net costs per LYG were subsequently estimated at €19,110 and the additional cost of rhDNase treatment at €1,736 per year. The authors conclude that taking into account the potential long-term benefits, rhDNase may be conceived a cost-effective option.

Suri et al (12) compared mean incremental costs of daily and alternate day rhDNase with hypertonic saline (HS) over a 12 week period as investigated in a clinical trial(66), in what they labelled themselves a cost-consequence analysis. The mean incremental costs of daily rhDNase compared with HS were €986 and the incremental cost of using daily over



alternate day rhDNase was €359. A formal cost-effectiveness analysis to analyse whether the increased effectiveness of daily rhDNase compared to HS twice daily delivered by nebulizer was not done. It was merely concluded that daily rhDNase was more expensive and significantly increases health care costs (12). Administering rhDNase on an alternate day rather than on daily basis may be as effective, with a potential cost saving.

In the study of Grieve et al (51) daily rhDNase was found to be more effective than HS and almost as effective as alternate day rhDNase. For a ceiling ratio of €140 per 1% gain in FeV<sub>1</sub>, the mean net benefits of daily and alternate daily rhDNase compared with HS were €811 and €832, respectively. The mean net benefit of alternate compared with daily rhDNase was €21. It was concluded that if decision makers were prepared to pay €140 per 1% gain in FeV<sub>1</sub> over a 12 week period (ceiling ratio), both rhDNase therapies may be conceived cost-effective.

Generally, the long-term perspective is often missing in these studies and they often only include the cost savings by reducing exacerbations and RTI's. Ergo, hospital admissions and reduced costs for antibiotic therapy were included, but direct costs for, for example, adverse drug reactions were not. Additionally, direct non-medical costs such as travelling to the health-care service, and indirect costs of productivity losses were not estimated. Finally, we note that only one study estimated net costs per LYG, and none estimated QALYs gained, despite the fact that important health-related quality-of-life effects exist.

## ECONOMIC ASPECTS OF RHDNASE DELIVERY SYSTEMS

The cost-effectiveness analysis done as mentioned above were all based on rhDNase administration via a nebulizer. As mentioned previously, the Dry Powder Inhalation (DPI) of rhDNase may offer advantages, in particular more efficient administration (table 2). Focussing at drug-delivery systems for patients with CF (for example, DPI vs. aerosol inhaler) no cost-effectiveness analysis was found. Potential advantages of a DPI of rhDNase are:

- An improved compliance to therapy,
- Improved (deep) lung deposition,
- No need for electricity or compressed air,
- A reduced administration time
- No need to cool the rhDNase-ampoule (29, 36, 56, 67, 68)

On the other hand, a short-coming of DPI's is that the patient's own inhalation strength is needed for the deposition of rhDNase in the lungs. This can be a problem for patients with severe CF-related symptoms and exacerbations.

Table 2. Advantages and disadvantages of DPI vs nebulization, partly taken from De Boer et al. (69)

Dry Powder Inhalation		Nebulization	
Advantages	Disadvantages	Advantages	Disadvantages
Less expensive	Performance depends on the patient's inspiratory flow profile	High dose uniformity	Expensive
Propellant free	Resistance of the device and other design parameters	Performance does not depend on the patient's inspiratory flow profile	Low deposition efficiency
High deposition efficiency	Potential difficulties to obtain dose uniformity		Long administration time
Short administration time (mobility)	Not worldwide available		Need for power supply or pressurized air (immobility)
Less potential problems with drug stability			Potential problems with drug stability
Less potential for extractables from device components			Large number of combinations of devices possible

To appreciate the economic aspects of delivery systems in general we note the study of Massie et al (70) comparing a nebulizer (aerosol delivery) with DPI in asthma. In this study it is mentioned that the equipment for aerosol delivery is costly (air compressor and nebulizer), less than 5% of the nebulized dose is actually delivered to the airway (relatively high wastage) and the duration of delivery confronts the patient with problems. These problems can negatively affect patients' adherence to the treatment. In short, the nebulization delivery may be an inefficient and relatively expensive delivery system, if DPI is available (70).

DPIs are self-actuating, provided that sufficient inspiratory flow is generated. DPIs are less expensive than nebulizers and they offer advantages in terms of better deposition, better disease control and the ease of use. The low cost of DPIs may be further decreased by a reduction in the number of costly complications and exacerbations, due to better compliance. Furthermore, DPIs enhance patient comfort. A drawback of DPI is the requirement for the ability to develop sufficient inspiratory flow, which is often impossible for children under the age of 6-8 years (70).

### EXPERT OPINION

CF is a costly disease, in which rhDNase is one of the therapeutic options. But the wastage of rhDNase and other disadvantages of nebulization make the therapy expensive. A better, efficient and easier delivery system for rhDNase can possibly improve efficiency and reduce wastage of rhDNase. For that reason, it could be more cost-effective than nebulization. From an ethical point of view it is better to provide rhDNase by DPI, since the adherence of patients to nebulization is quite low as described by Burrows (64). Low adherence results in in-effective therapy and could lead to increased costs. This can be one of the reasons why DPI could be more cost-saving than nebulized rhDNase. Other advantages of DPI like the absence of the need for electricity, easier usage and more efficient delivery of rhDNase (compared to the nebulization) are also relevant with respect to potential cost-savings of rhDNase therapy.

For drugs which have a significant impact on the total health care budget, large efforts should be made to develop an adequate dosage form. In this way, innovative research is stimulated which potentially results in lower cost as can be proved with rhDNase. However, the focus when introducing

a new drug is primarily directed toward the regulatory agencies and their requirements regarding efficacy and safety, which is completely understandable for reasons of public protection. On the other hand, the horizon should be put beyond the regulatory hurdle and put to the group of patients who are to receive the new drug. If beforehand it is already known that compliance is a problem with a certain dosage form, action should be taken to avoid that problem. At the time of introduction of rhDNase to the market, the technology to create a dry powder of labile substances was not fully available. However, this technology has improved over the past decade and is readily available. Moreover, DPI technology has improved meanwhile. Therefore, DPI is now an option when such drugs are developed. This gives rise to great opportunities, as for example shown by insulin (71-74).

Our opinion is that DPI will gain a greater share in the field of inhalation due to obvious reasons like patient adherence, ease of use, efficiency and cost-effectiveness. As mentioned in chapter 2, the deposition efficiency of DPI may be 4- to 6-fold that of a nebulizer (28, 35, 36). For illustrative purposes we crudely estimated cost-effectiveness outcome of once-daily DPI rhDNase administration based on McIntyre (14), in which net costs per LYG for once-daily aerosol delivery were estimated at € 19,110 in the baseline. Due to higher deposition efficiency of DPI, we conservatively assumed that for DPI delivery 30% less rhDNase is necessary to reach at least the same benefits and effectiveness as in delivery by nebulizer (14, 16). Then, for DPI rhDNase therapy net costs per LYG may be estimated at € 12,100. This corresponds with a reduction in the cost-effectiveness ratio of almost 40% for DPI delivery of rhDNase compared to delivery by means of nebulization. Incremental cost-effectiveness for DPI over nebulization may then be estimated at € 5,100.

## FIVE-YEAR VIEW

With respect to the cost-effectiveness analysis in rhDNase (aerosol-delivery) treatment, gaps were detected in the methods and cost components included. For the future it is advisable to carry out a cost-effectiveness analysis in which all cost components (direct and indirect) are included and the outcome should preferably be expressed in costs per Quality Adjusted Live Year (QALY) or costs per life-year gained. Extrapolating from short-term results in clinical trials to long-term pharmaco-economic outcomes, for example, life-years gained, requires

modelling within an adequately chosen time frame. Such a model should include up to date epidemiological data, for example, from CF-registries that exist for several countries, such as the Netherlands.

It may be estimated that DPI will result in better adherence to the expensive therapy. The higher deposition efficiency of DPI compared to nebulization will result in a cost-reduction. Furthermore, to nebulize a drug there are numerous options to choose from considering only the numerous available nebulizing techniques and nebulizers. Moreover, these different nebulizers have different performances with respect to the rate of nebulization and the characteristics of the aerosol they create. For the physician it is difficult to choose an appropriate nebulizer which gives an appropriate particle size distribution. In contrast, a DPI is developed alongside with the formulation. This means that the inhalator is specifically designed to give the best result in terms of de-agglomeration of the formulation. The inhalator is so to say “dedicated” to the specific formulation. For the physician it has advantages and the patient eventually benefits most of DPI. It is expected that DPI-use will increase over the next period and that nebulization will still be a therapeutic option for a small number of drugs. For high-cost medication, such as rhDNase, it will be more likely to be developed as a DPI, as the cost-reduction may be expected to have the greatest impact compared to nebulization for these drugs.

### Key Issues

Patients with Cystic Fibrosis have thick, tenacious sputum. They are chronically colonized with bacteria. This leads to frequent exacerbations and is a burden for these patients. Of the patients which are hospitalized each year (around 33%), 75% is treated for pulmonary infections.

Recombinant human Deoxyribonuclease I (rhDNase) is a protein which has beneficial effects on lung function ( $FEV_1/FVC$ ) and number of hospitalizations.

RhDNase is currently administered by nebulization which is an inefficient method of administration. Dry powder inhalation of rhDNase is almost available and is likely to be more effective than nebulization.

In this review we investigated the pharmacoeconomic effect of dry powder inhalation versus nebulization of rhDNase.

We performed an extensive review of the available literature but scarce information about pharmacoeconomics of rhDNase is available. It was

found that rhDNase does have a moderate effect and that dry powder inhalation can possibly be cost-saving with the same efficacy as obtained by nebulization.

We conservatively assumed that for DPI delivery 30% less rhDNase is necessary to reach at least the same benefits and effectiveness as in delivery by nebulizer. This corresponds with a reduction in the cost-effectiveness ratio of almost 40% for DPI delivery of rhDNase compared nebulization.

We hypothesize that the patients benefit most from dry powder inhalation due to increased mobility and ease of use. It is expected that DPI-use will increase over the next period and that nebulization will still be a therapeutic option for a small number of drugs. For high-cost medication, like rhDNase, it will be more likely to be developed as a DPI, since there might be a cost-reduction compared to nebulization.

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