TITLE: Dornase Alfa for Patients with Cystic Fibrosis: A Review of the Clinical Efficacy and Cost-Effectiveness

DATE: 25 June 2013

CONTEXT AND POLICY ISSUES

In Canada, one in every 3,600 newborns is diagnosed with cystic fibrosis (CF) and approximately half of these individuals are diagnosed by six months of age. Furthermore, with no known cure, one Canadian dies from CF each week with a median age of survival of 48.5 years. The primary cause of morbidity and mortality among CF patients is pulmonary disease. The management of CF pulmonary disease requires a multidisciplinary approach with numerous treatment options including digestive enzyme supplements, dietary changes, medications, and physiotherapy.

Cystic fibrosis, as defined by Flume et al., is “a recessive genetic disease characterized by dehydration of the airway surface liquid and impaired mucociliary clearance”. Disease severity for CF is based on lung capacity measured by spirometry pulmonary function tests such as forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC). Normal pulmonary disease is defined as FEV1 percentage of greater than 90% predicted, 70-89% predicted for mildly impaired, 40-69% predicted for moderately impaired, and an FEV1 percentage of less than 40% predicted is defined as severely impaired.

Dornase alfa (Pulmozyme) is a purified solution for inhalation of recombinant human deoxyribonuclease (rhDNase) which reduces lung sputum viscosity and improves secretion clearance. Dornase alfa is recommended for the chronic treatment of moderate to severe CF pulmonary disease. For patients with at least one copy of the G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, treatment with ivacaftor is recommended with a dose of 150 mg orally every 12 hours with fat-containing foods. The Canadian Drug Expert Committee (CDEC) recommends that ivacaftor be listed for the treatment of CF in patients age six years and older who have a G551D mutation, with the of a substantial reduction in price and that clinical criteria for the discontinuation of ivacaftor treatment in patients who fail to demonstrate a meaningful response be developed in consultation with CF treatment clinics. Hypertonic saline inhalation has shown to increase hydration of airway surface liquid in CF patients and its use has been recommended for use to improve lung
function and reduce exacerbations. With a lack of well-designed comparative studies, there is an uncertainty of when to prescribe dornase alfa or other treatment options such as hypertonic saline as guidelines have not assigned priorities over these treatments.

With the various treatment options for CF pulmonary disease, a thorough understanding of the clinical and cost-effectiveness of these treatments used concomitantly or individually is needed. The purpose of this review is to examine the clinical and cost-effectiveness of dornase alfa, as well as its comparative efficacy compared to ivacaftor for the treatment of CF.

RESEARCH QUESTIONS

1. What is the clinical efficacy of dornase alfa for the treatment of patients with cystic fibrosis?

2. What is the comparative clinical efficacy of dornase alfa compared with ivacaftor for the treatment of patients with cystic fibrosis?

3. What is the cost-effectiveness of dornase alfa for the treatment of patients with cystic fibrosis?

KEY FINDINGS

Dornase alfa appears to be effective in improving lung function among patients with CF when compared to placebo. There was no evidence of the comparative efficacy of dornase alfa and ivacaftor for the treatment of CF. With a limited amount of evidence, the cost effectiveness of dornase alfa for the treatment of CF remains to be established.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Embase, The Cochrane Library (2013, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval to study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2003 and May 30, 2013.

Selection Criteria and Methods

One reviewer screened citations to identify publications that met the inclusion criteria. Potentially relevant articles were retrieved based on the review of titles and abstracts. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1. Rapid Response reports are organized so that the evidence for each research question is presented separately.

Dornase Alfa for Cystic Fibrosis
Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with cystic fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Dornase Alfa (Pulmozyme) alone or in combination with other treatments</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo, hypertonic saline solutions, Ivacaftor (Kalydeco) alone or in combination with other treatments</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical efficacy, Cost-effectiveness</td>
</tr>
<tr>
<td>Study Designs</td>
<td>HTA/ Systematic review/Meta-analysis, Randomized controlled trials, Economic evaluation</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, or were full text articles published prior to January 2003. Health technology assessments, meta-analyses, and systematic reviews were excluded if there was incomplete reporting of methods or if they were superseded by a more recent or more rigorous review or guideline. Randomized controlled trials (RCTs) were excluded if they were described in a systematic review included in this report. Economic evaluations were excluded if they were not cost-effectiveness or cost-utility analyses.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised and summarized narratively. The methods used when conducting the literature search, study selection, quality assessment, data extraction, and summarizing the data were appraised for the systematic review using the AMSTAR instrument and RCTs were appraised using the with Scottish Intercollegiate Guidelines Network (SIGN50) methodology checklist. The economic evaluation was assessed using the 35-item Drummond’s checklist. A numeric score was not calculated for each study. Instead, the strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 136 citations. Upon screening titles and abstracts, 115 citations were excluded and 21 potentially relevant articles were retrieved for full-text review. No additional potentially relevant reports were retrieved from the grey literature and by hand search. Of the 21 potentially relevant reports 18 were excluded. One systematic review report, one RCT, and one economic evaluation met the inclusion criteria. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

Clinical efficacy of dornase alfa for CF

A summary of the study characteristics can be found in Appendix 2.
Systematic Review

The systematic review by Jones et al. was published in 2010.4 Fifteen RCTs, published between 1993 and 2004, were included in the systematic review. The included studies involved 2469 patients, comparing dornase alfa to placebo, no dornase alfa treatment, and hypertonic saline. The duration of the included studies ranged from six days to three years. The majority (8 out of 15) of trial durations were less than 12 weeks (one lasted three months, one lasted six months, one lasted nine months, two lasted one year, one lasted two years, and the longest lasted three years). The dornase alfa dose ranged from 0.6 mg to 10 mg, either once or twice daily. Seven of fifteen included studies in the systematic review used dornase alfa 2.5mg once daily, which is the dose approved by Health Canada. A normal saline solution was used as placebo in two trials, while five trials stated that the placebo used was excipient alone. Three trials did not provide a formal definition of the placebo used. The severity of pulmonary disease varied across studies (FVC from 35% to over 80%). Participants were over the age of 5 years in all included studies (maximum age was not provided). The authors did not provide insight on the use of concomitant medications during the trials. Main clinical efficacy outcomes included FEV1, FVC, mean number of exacerbations, and mortality.

Randomized controlled trial

In the RCT with cross-over design by Amin et al.10 nineteen patients with a confirmed diagnosis of CF and mild pulmonary disease, between the ages of 6 to 18 years, a baseline FEV1 ≥ 80%, an oxyhaemoglobin saturation of ≥ 90% on room air, and who were able to perform reproducible spirometry were randomized to receive four weeks of dornase alfa 2.5mL or placebo 2.5mL inhalation. Aside from the exclusion criteria of current oral corticosteroid use, oxygen supplementation, intravenous antibiotics or quinolones 14 days prior to enrolment, investigational drugs 30 days prior to enrolment, the use of concomitant medications was not reported. The trial consisted of two, 4-week treatment periods separated by a 4-week washout. Over half (58%) of the participants were female with a mean age (± standard deviation (SD)) of 10.3 ± 3.4 years. The total duration of the study was twelve weeks. Outcomes included lung clearance index (LCI) scores, where an increased score represents ventilation inhomogeneity during multiple breath washout. Spirometry parameters such as predicted change in FEV1, FVC, and forced expiratory flow at 25–75% of FVC (FEF25-75%) were also measured during the 4 week treatment periods.

Comparative clinical efficacy of dornase alfa vs. ivacaftor for CF

No evidence for the clinical efficacy of dornase alfa compared to ivacaftor for CF was found

Cost-effectiveness of dornase alfa

Economic evaluations

An economic evaluation by Grieve et al.11 was performed alongside an open randomized cross-over trial12 included in the systematic review by Jones et al.4 The authors compared the relative cost-effectiveness of daily dornase alfa, with alternate day dornase alfa and hypertonic saline for the treatment of CF among children. Health service costs were calculated by multiplying unit costs to health resource use over the 12-week treatment period. Cost-effectiveness was presented by the nonparametric bootstrap method, acceptability curves, and net benefit statistics for each treatment comparison.
The systematic review by Jones et al.\textsuperscript{4} provided a brief overview of three studies, performed in Germany and the United States, that examined the cost of health care for participants in an American multicenter study for dornase alfa\textsuperscript{13} included in the systematic review. These studies were published between 1995 and 1996. One study\textsuperscript{14} estimated the mean total cost of respiratory tract infection related care which included outpatient antibiotic therapy and inpatient care cost estimates. Another study\textsuperscript{15} used the same data but performed an analysis of costs of therapy which included inpatient admission, outpatient appointments and investigations costs. This study did not include the cost of dornase alfa as it was not yet marketed during the trial, but performed the analysis as if patients were treated in a German CF centre. Similarly, Menzin et al.\textsuperscript{16} performed an analysis which excluded dornase alfa costs, but estimated the reduction in cost of respiratory tract infection-related care in the UK, France, Italy and Germany. Respiratory tract infection related healthcare costs were estimated in Oster et al.\textsuperscript{14} Estimated costs included hospitalization and outpatient antibiotic treatment, but excluded costs of dornase alfa as it was not yet marketed during the time of the trial. The provided costs for each group were US $6,443 for the placebo (excipient alone) group, US $4,761 for the once-daily dosage regimen group, and US $5,628 for the twice-daily dosage regimen group. Estimates including dornase alfa costs were later produced after it was marketed with a cost of US $27 per ampoule, revealing an offset between 18.3\% and 37.5\% of the cost of therapy for respiratory tract infection related care. Von der Schulenburg et al.\textsuperscript{15} described costs for placebo (US $4,742) and the once-daily dosage regimen (US $3,551). The results in Menzin et al.\textsuperscript{16} demonstrated variations in cost reductions due to differences in medical practice among the European countries. Cost reductions ranged from US $700 in the UK to US$ 2,100 in France. These three studies do not meet the inclusion criteria of this review as they were published prior to January 2003.

Summary of Critical Appraisal

The strengths and limitations of included studies are summarized in Appendix 3 and Appendix 4. The systematic review by Jones et al.\textsuperscript{4} met most AMSTAR criteria and is considered to be of high methodological quality. A comprehensive literature search was performed and study selection and data extraction were performed by two independent reviewers. A list of included and excluded studies was provided and the scientific quality of the included studies was assessed and documented. The systematic review was limited by the heterogeneity and low methodological quality of the included studies. The study by Amin et al.\textsuperscript{10} was of high methodological quality meeting most requirements of the SIGN 50 checklist. The research question was clearly defined, the double blinding process was clearly described, and there were no drop-outs. The randomization method was clearly described and allocation concealment was reported. One concern was the differences in baseline lung clearance index scores, the primary outcome, prior to the placebo and dornase alfa treatments.

The economic evaluation report was considered to be of high methodological quality as per the Drummond checklist. The research question was well defined and the analysis method was clearly stated. The key parameters on which the analysis was based were justified and the sample size and time horizon were clearly specified. A limitation was that the cost-effectiveness analysis was based on one RCT which may have been subject to bias as participants were not blinded, and there was uncertainty regarding incomplete outcome data and selective reporting. The time horizon of the study, 12 weeks, is relatively short, thus the long-term cost effectiveness of the selected treatments is unclear.
Summary of Findings

Systematic Review

Main findings from the systematic review by Jones et al.⁴ can be found in Appendix 5. Four trials provided data for mean percentage change in FEV1 (n= 248, mean difference [MD] 8.36 (95% confidence interval [CI] 0.33 to 16.40) and mean percentage change in FVC (MD 7.52, 95% CI 1.34 to 13.69) at one month. One trial reported mean percentage change in FEV1 (n= 320, MD 7.30, 95% CI 4.04 to 10.56) and mean percentage change in FVC (MD 5.10, 95% CI 1.23 to 8.97) at three months among subjects with severe lung disease. One trial reported mean percentage change in FEV1 (n= 647, MD 5.80, 95% CI 3.99 to 7.61) and FVC (MD 3.80, 95% CI 2.62 to 4.98) for the once daily treatment group at six months. Among the twice daily treatment groups, mean percentage change in FEV1 was (MD 5.60, 95% CI 4.90 to 6.29) and FVC (MD 3.00, 95% CI 1.82 to 4.18) at six months. At one year, percentage change from baseline in FEV1 was measured in one trial (n=25, MD 4.10, 95% CI 4.10 to 12.20). One trial reported results of absolute increases of FEV1 (n= 410, MD 3.24, 95% CI 1.03 to 5.45) and FVC (MD 0.70, 95% CI -1.24 to 2.64) at two years. One trial (n=85) did not report any significant differences in lung function parameters over three years (results not provided).

At three months, one study (n=320) reported a non-statistically significant age adjusted risk ratio (RR) of having more than one respiratory exacerbation during the trial (RR 0.93, 95%CI 0.69 to 1.21). At six months, one study (n=647) the age adjusted risk ratios for having more than one exacerbation during the trial was 0.72 (95% CI 0.52 to 0.98) for the once-daily group and 0.63 (95% CI 0.46 to 0.87) for the twice-daily group. At two years, one study (n=410) presented a RR of 0.71 (95% CI 0.49 to 1.02) for having more than one exacerbation which was not statistically significant.

The difference in number of deaths between groups was not significant. At one month, of the five trials which reported mortality (n=253), only one trial reported two deaths among the dornase alfa treatment group. At three months, one trial (n= 320) reported an odds ratio (OR) of 1.57 (95% CI 0.55 to 4.52) for the dornase alfa treatment group. At six months, one study (n=647) reported an OR of 1.01 (95% CI 0.06 to 16.21) as one death occurred in both the treatment and control group. No deaths were reported in one study (n=410) at two years.

Hence, the evidence from this systematic review proposes that treatment with dornase alfa over a one month and six month duration improves lung function in CF patients. Dornase alfa also significantly improved FEV1 over a two-year period.

Randomized controlled trial

The RCT by Amin et al.¹⁰ (n=19) revealed greater absolute changes in LCI scores among the dornase alfa group (MD 0.71, 95% CI 0.12 to 1.3) compared to placebo (MD 0.31, 95% CI 0.33 to 0.95). The authors used a mixed model to adjust for baseline characteristics and to obtain unbiased treatment effects. Results of the mixed model revealed improved LCI scores with a treatment effect (±SD) of -0.90 ± 1.44 (P=0.02) and FEF25-75% with a treatment effect (±SD) of 6.09 ± 10.34 (P=0.03) after four weeks of dornase alfa compared to placebo. Treatment effects for predicted FEV1 [0.076 ± 8.43 (P=0.97)] and FVC [-0.90 ± -3.61 (P=0.14)] were not statistically significant. These results suggest dornase alfa has favourable effects compared to placebo when using measures and parameters that are sensitive to small airways.
Economic evaluation

The cost-effectiveness analysis by Grieve et al.\textsuperscript{11} reported health service unit costs based on the British National Formulary using 1999-2000 prices. The daily dornase alfa group had the highest mean (SD) total costs £5,694 (3,377), followed by the alternate day dornase alfa group £5,230 (3,737), and the hypertonic saline group £4,285 (3,903). Hospital admissions and total inpatient days were highest among the alternate day dornase alfa group, while outpatient visits and nurse contacts were highest among the hypertonic saline group. General practitioner contacts were highest in the daily dornase alfa group (Table 2). Incremental cost-effectiveness ratios (ICERs) (£ per 1% gain in FEV1) were highest between the daily and alternate day dornase alfa treatments, and lowest between the alternate day dornase alfa and hypertonic saline treatments (Table 3). With a ceiling ratio of £200 per 1% gain in FEV1, the mean net benefits of daily and alternate day dornase alfa compared with hypertonic saline were £1,158 (95% CI –621 to 2,842) and £1,188 (95% CI –847 to 3,343), respectively. The mean net benefit of daily compared with alternate day dornase alfa was £30 (95% CI, –£2,091 to 1,576). With this same ceiling ratio, the cost effectiveness acceptability curves demonstrated that the probability of cost-effectiveness for daily dornase alfa is 0.91 and 0.88 for alternate day dornase alfa when compared with hypertonic saline. Therefore, results suggest that dornase alfa used in daily or alternate day regimens are cost-effective compared to hypertonic saline if decision makers are prepared to pay £200 for a 1% gain in FEV1 over a 12-week period.

Table 2: Mean (SD) Resource Use and Total Costs (£)

<table>
<thead>
<tr>
<th>Resource</th>
<th>Hypertonic saline n=40</th>
<th>Daily dornase alfa n=40</th>
<th>Alternate day dornase alfa n=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admissions</td>
<td>0.53 (0.75)</td>
<td>0.63 (0.87)</td>
<td>0.80 (1.07)</td>
</tr>
<tr>
<td>Total inpatient days (no. days)</td>
<td>5.13 (8.84)</td>
<td>4.73 (7.73)</td>
<td>5.65 (7.70)</td>
</tr>
<tr>
<td>Outpatient visits (no. visits)</td>
<td>1.23 (1.10)</td>
<td>0.93 (1.07)</td>
<td>0.83 (0.81)</td>
</tr>
<tr>
<td>GP contacts (no. contacts)</td>
<td>0.25 (0.49)</td>
<td>0.30 (0.61)</td>
<td>0.18 (0.38)</td>
</tr>
<tr>
<td>Nurse contacts (no. contacts)</td>
<td>2.70 (10.12)</td>
<td>1.75 (6.65)</td>
<td>2.38 (7.91)</td>
</tr>
<tr>
<td>Total cost (£)</td>
<td>4,285 (3,903)</td>
<td>5,694 (3,377)</td>
<td>5,230 (3,737)</td>
</tr>
</tbody>
</table>

Table 3: Mean Incremental Cost, Incremental Effectiveness, and Net Benefit over 12 Weeks (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Hypertonic saline n=40</th>
<th>Daily dornase alfa n=40</th>
<th>Alternate day dornase alfa n=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost (£)</td>
<td>1,409 (354 to 2,277)</td>
<td>464 (−647 to 1,510)</td>
<td>945 (−509 to 2,301)</td>
</tr>
<tr>
<td>Effectiveness (% FEV1)</td>
<td>14 (5 to 23)</td>
<td>2 (−6 to 12)</td>
<td>12 (2 to 22)</td>
</tr>
<tr>
<td>ICER (£ per 1% gain in FEV1)</td>
<td>110</td>
<td>214</td>
<td>89</td>
</tr>
<tr>
<td>Mean net benefit (£)</td>
<td>3,725 (585 to 6,701)</td>
<td>403 (−3,303 to 3,341)</td>
<td>3,321 (−116 to 6,976)</td>
</tr>
</tbody>
</table>

FEV1= forced expiratory volume in 1 second; ICER= incremental cost-effectiveness ratio; Rc=ceiling ratio

Limitations

Although the methodological quality of the systematic review by Jones et al.\textsuperscript{4} was high, there were limitations affecting external validity. The majority of the studies were short-term (less than 1 month) and do not provide insight on long-term effects. The duration of one included study was only six days, thus efficacy results over such a short duration may not be valid. There was
a risk of bias seen among the included studies. Only two of the fifteen included studies provided adequate descriptions of allocation concealment. In addition, the majority of studies did not provide details on blinding procedures. Heterogeneity was statistically significant among the included studies measuring FEV1 (P<0.001) and FVC (P=0.02) as the authors included a wide range on inclusion criteria (different doses and subjects with varying severity of lung disease). Results of this systematic review therefore need to be interpreted with caution.

The RCT by Amin et al.10 was limited by its small sample size (n=19) which is reflective of the specific exclusion criteria. This study was powered to measure differences in LCI measurements, and not the secondary outcomes of FEV1 and FVC. The generalizability of the results is limited as the trial was carried out at a single site in the United Kingdom, and the sample size was powered according to a specific population, school age children with CF from the UK. One concern in this trial was the differences in baseline measures prior to the intervention. The LCI scores were significantly worse prior to placebo therapy than dornase alfa. Although subjects were randomized accordingly, variation between the two groups likely occurred. While the authors used a mixed model to adjust for this variation, results should still be carefully interpreted.

The cost-effectiveness reported in Grieve et al.11 may not be generalizable to costs presently seen in Canada as the authors used prices from the British National Formulary in 1999-2000. The analysis revealed that the results are highly sensitive to the price of treatment, thus results may not be accurate for present-day costs of dornase alfa. In addition, indirect costs related to lost productivity of patients/caregivers were not included in the analysis.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Compared placebo and hypertonic saline, dornase alfa resulted in improved spirometric lung function, measured with FEV1 and FVC, with significant differences at one month, three months and two years in the treatment of children and adults with CF. Dornase alfa produced a non-significant reduction in the risk of infective exacerbations and the difference in the number of deaths between treatment groups was not significant. These findings must be interpreted with caution due to the methodological limitations and clinical heterogeneities of the included studies. Given the lack of quality of the included RCTs in the systematic review, there is a need for long-term high quality trials to compare the efficacy of dornase alfa with other CF treatments. Based on the results of a single study, dornase alfa appears to more effective compared to placebo when measuring ventilation inhomogeneity using the LCI measure. No evidence was found to assess the comparative effectiveness between dornase alfa and ivacaftor. The limited evidence revealed that providing dornase alfa on an alternate-day basis may be the more cost-effective than hypertonic saline or providing dornase alfa daily. These findings may not be reflective of present Canadian costs, thus more cost-effectiveness analyses, with long-term perspectives are needed. Cost-effectiveness analyses should also consider including indirect costs such as productivity losses, providing accurate measurements of the economic burden of CF.

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REFERENCES


2. Simon RH. UpToDate [Internet]. UpToDate. Cystic fibrosis: overview of the treatment of lung disease; 2013 [cited 2013 Jun 3].


APPENDIX 1: Selection of Included Studies

136 citations identified from electronic literature search and screened

115 citations excluded

21 potentially relevant articles retrieved for scrutiny (full text, if available)

No potentially relevant reports retrieved from other sources (grey literature, hand search)

21 potentially relevant reports

18 reports excluded:
- irrelevant population (2)
- irrelevant intervention (3)
- irrelevant comparator (2)
- irrelevant outcomes (4)
- already included in the selected systematic reviews (5)
- other (review articles, editorials) (2)

3 reports included in review
## APPENDIX 2: Characteristics of Included Clinical Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design/ Length of Follow-up</th>
<th>Patient Characteristics, Sample Size (n)</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic review</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones* 2010, United Kingdom</td>
<td>N=15 studies included in the systematic review; 6 days to 3 years</td>
<td>Children and adults with CF, at all stages of lung disease (n=2469)</td>
<td>Dornase alfa at any dose, using any nebulizer, any frequency and duration</td>
<td>Placebo or any other mucolytic</td>
<td>FEV1, FVC, exacerbations, mortality</td>
</tr>
<tr>
<td><strong>RCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amin 2011 Canada</td>
<td>RCT 12 weeks</td>
<td>Patients with a confirmed diagnosis of CF and mild pulmonary disease, between the ages of 6 to 18 years19, female: 54%; Age: mean(SD): 10.3±3.4 years</td>
<td>Dornase alfa (2.5mL)</td>
<td>Placebo (excipient alone) (2.5mL)</td>
<td>LCI, FEV1, FVC</td>
</tr>
</tbody>
</table>
## APPENDIX 3: Summary of Study Strengths and Limitations

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Systematic Review assessed with AMSTAR² | • Research questions and selection criteria were defined and presented  
• Comprehensive literature search based on pre-defined criteria  
• Two independent investigators performed study selection, and data extraction  
• List of included studies provided  
• Quality assessment of the included studies was described  
• Methods used to combine the findings was clearly reported  
• Publication bias was assessed  
• Conflict of interest declared  
• List of excluded studies was provided | • Significant amount of heterogeneity among included trials.  
• Included trials were of low methodological quality |

| Amin ¹⁰ 2011 Canada | • Research question was clearly defined  
• Double blinding process was clearly described  
• No drop-outs  
• Randomization method was clearly described  
• Allocation concealment was reported. | • Variation in LCI scores (primary outcome) between groups at baseline  
• Small sample size (n=19) |

LCI- lung clearance index
## APPENDIX 4: Critical Appraisal of Included Economic Evaluation

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Grieve 11 2003, United Kingdom         | • Research question was well defined.  
                                         • The analysis method was clearly stated  
                                         • The key parameters on which the analysis was based were justified.  
                                         • Sample size and time horizon was clearly specified.  
                                         • Conflict of interest was declared. | • The analysis was based on a single non-blinded RCT, which was not powered to show a difference in healthcare utilization.  
                                         • Costs based on 1999-2000 from the BNF and are not reflective of present-day Canadian costs  
                                         • 12 week time horizon is relatively short. Results beyond 12 weeks must be extrapolated carefully.  
                                         • Indirect cost related to lost productivity of patients/caregivers was not included. |

BNF= British National Formulary; RCT=randomized controlled trial.
APPENDIX 5. Summary of Findings from Jones et al.4

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of trials</th>
<th>Number of participants (n)</th>
<th>Dornase alfa vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean percentage changes in FEV1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At one month</td>
<td>4</td>
<td>248</td>
<td>MD 8.36 (0.33 to 16.40)</td>
</tr>
<tr>
<td>At three months</td>
<td>1</td>
<td>320</td>
<td>MD 7.30 (4.04 to 10.56)</td>
</tr>
<tr>
<td>At six months</td>
<td>1</td>
<td>647</td>
<td>MD 5.80 (3.99 to 7.61) (once daily treatment group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MD 5.60 (4.90 to 6.29) (twice daily treatment group)</td>
</tr>
<tr>
<td>At one year</td>
<td>1</td>
<td>25</td>
<td>MD 4.10* (4.10 to 12.20)</td>
</tr>
<tr>
<td>At two years</td>
<td>1</td>
<td>410</td>
<td>MD 3.24** (1.03 to 5.45)</td>
</tr>
<tr>
<td><strong>Mean percentage changes in FVC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At one month</td>
<td>4</td>
<td>248</td>
<td>MD 7.52 (1.34 to 13.69)</td>
</tr>
<tr>
<td>At three months</td>
<td>1</td>
<td>320</td>
<td>MD 5.10 (1.23 to 8.97)</td>
</tr>
<tr>
<td>At six months</td>
<td>1</td>
<td>647</td>
<td>MD 3.80 (2.62 to 4.98) (once daily treatment group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MD 3.00 (1.82 to 4.18) (twice daily treatment group)</td>
</tr>
<tr>
<td>At two years</td>
<td>1</td>
<td>410</td>
<td>MD 0.70** (-1.24 to 2.64)</td>
</tr>
<tr>
<td>&gt;1 respiratory exacerbation during the trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At three months</td>
<td>1</td>
<td>320</td>
<td>RR 0.93 (0.69 to 1.21)</td>
</tr>
<tr>
<td>At six months</td>
<td>1</td>
<td>647</td>
<td>RR 0.72 (0.52 to 0.98) (once daily treatment group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR 0.63 (0.46 to 0.87) (twice daily treatment group)</td>
</tr>
<tr>
<td>At two years</td>
<td>1</td>
<td>410</td>
<td>RR 0.71 (0.49 to 1.02)</td>
</tr>
</tbody>
</table>

*Based on percentage change from baseline
** Reported as absolute differences
FEV1=forced expiratory volume at one second; FVC= forced vital capacity; MD=Mean difference; RR=risk ratio