Human $\alpha_1$-Proteinase Inhibitor for Patients with $\alpha_1$-Antitrypsin Deficiency
Until April 2006, the Canadian Agency for Drugs and Technologies in Health (CADTH) was known as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).


This report and the French version entitled Inhibiteur de la protéinase alpha-1 humaine pour les patients ayant un déficit en alpha-1 antitrypsine are available on CADTH’s web site.

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Human $\alpha_1$-Proteinase Inhibitor for Patients with $\alpha_1$-Antitrypsin Deficiency

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Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, and procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a systematic review would be required to meet their needs.

The systematic review was prepared by two internal HTIS reviewers in consultation with two clinical experts. Research questions and selection criteria were developed jointly by the two HTIS reviewers and the clinical experts. The literature search was carried out by an information specialist using a defined search strategy.

Each HTIS reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

The draft was written by the research team with input from external clinical experts. The draft was also externally peer reviewed. The draft was finalized based on the input received.
Human $\alpha_1$-Proteinase Inhibitor for Patients with $\alpha_1$-Antitrypsin Deficiency

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Conflict of Interest

Kenneth Chapman, has consulted with or received grants from 3M, Altana, Amgen, AstraZeneca, Bayer, Biovail, Boehringer Ingelheim, Genpharm, GlaxoSmithKline, Hoffmann-La Roche, Merck Frosst, Novartis, Pfizer, Schering-Plough, Talecris, Theratechnologies.

No conflicts of interest were declared by the other reviewers and authors.
Human $\alpha_1$-Proteinase Inhibitor for Patients with $\alpha_1$-Antitrypsin deficiency

Technology and Condition
Human $\alpha_1$-proteinase inhibitor ($\alpha_1$-PI) intravenous infusion for patients with $\alpha_1$-antitrypsin (AAT) deficiency, with or without a diagnosis of chronic obstructive pulmonary disease.

Issue
Public funding of $\alpha_1$-PI varies across Canada. There is still uncertainty about its beneficial and harmful effects on health, its associated costs, and how the drug should be funded and accessed.

Methods and Results
A systematic review of clinical and economic literature was conducted. Information regarding funding and delivery in Canada and similar, public health systems was collected and synthesized. One randomized controlled trial, four retrospective cohort studies, and eight case series reports provided evidence of clinical effect. Three cost-effectiveness and two cost studies conducted outside Canada were identified.

Implications for Decision Making
- **Evidence showing health improvement is inconclusive.** In controlled trials, augmentation therapy has not shown reduced lung function impairment in patients with AAT deficiency and COPD, compared with normal care. Conversely, in observational studies, $\alpha_1$-PI is associated with outcomes suggestive of therapeutic benefit in patients with severe AAT deficiency and moderate airflow obstruction. Severe adverse events from treatment have been reported in ~1% of study populations.
- **Use in patients without COPD is experimental.** No evidence was found evaluating the use of $\alpha_1$-PIs in patients with AAT deficiency and no lung function impairment.
- **Anticipated health gains may cost more than other funded treatments.** Based on the only cost-utility analysis conducted, lifetime costs could average almost US$1 million to produce 2.57 QALYs (from 4.62 with standard care to 7.19) resulting in a ratio of US$333,349 for a QALY. It is anticipated that Canadian costs would be similar.
EXECUTIVE SUMMARY

Title: Human $\alpha_1$-Proteinase Inhibitor for Patients with $\alpha_1$-Antitrypsin Deficiency

Date: December 12, 2005

Context and Policy Issues

$\alpha_1$-antitrypsin (AAT) is a circulating proteinase inhibitor. Insufficient AAT in the human body predisposes individuals to the development of a rare form of chronic obstructive pulmonary disease (COPD), early onset panlobular emphysema, and less commonly, bronchiectasis. It is also associated with liver disease, and rarely, other organ disorders.

Treatment with $\alpha_1$-proteinase inhibitor ($\alpha_1$-PI), the augmentation therapy that is also known as $\alpha_1$-antitrypsin, is recommended for patients with severe AAT deficiency and with evidence of significant obstructive lung disease. Eligible patients must have quit smoking and received optimal medical therapy. The aim of this treatment is to restore the level of AAT, and prevent or slow the progress of emphysema. Commercially available $\alpha_1$-PI that are licensed internationally include Prolastin® (Talecris Biotherapeutics, Clayton NC), Aralast™ (Baxter, Deerfield IL), and Zemaira™ (ZLB Behring, King of Prussia PA). All products are produced from pooled human plasma. Only Prolastin has received regulatory approval in Canada (in 1988). In Canada, it is indicated for “chronic replacement therapy of individuals having congenital deficiency of $\alpha_1$-PI with clinically demonstrable panacinar emphysema.” It is generally infused at a dose of 60 mg/kg intravenously every week. The augmentation therapy that is reviewed in this report is only intended for the treatment of the pulmonary sequelae of AAT deficiency.

Public funding of Prolastin varies across provincial and territorial jurisdictions. There is uncertainty about the overall benefit, harm, and costs of $\alpha_1$-PI when it is used in patients with AAT deficiency or its associated chronic obstructive lung disease, and how the drug should be funded and accessed in Canada.

Research Questions

1. What is the evidence for clinical effectiveness (improved health outcomes, improved intermediate outcomes, and reduced harm) of human $\alpha_1$-PI compared with no human $\alpha_1$-PI in patients with AAT deficiency, and with or without a diagnosis of COPD?
2. What is the evidence of cost-effectiveness of using human $\alpha_1$-PI compared with no human $\alpha_1$-PI in patients with AAT deficiency?
3. What is the status of $\alpha_1$-PI in publicly funded drug plans in Canada?
4. In similar health jurisdictions outside Canada (US, New Zealand, Australia, and Europe), how is $\alpha_1$-PI funded?

Methods

Published English literature was obtained by searching BIOSIS Previews®, EMBASE®, and MEDLINE® databases on the DIALOG® search system from 1990 to September 2005. Regular alerts were established on all databases, and information from the alerts is current to December 2, 2005. Parallel searches were performed on PubMed and the Cochrane Library databases. Web sites of regulatory agencies, and health technology assessment and related agencies were also searched, as were specialized databases, such as those of the University of York Centre for Reviews and Dissemination. The Google™ and Yahoo™ search engines were used to search for information on the Internet. These searches were supplemented by hand searching the bibliographies of selected papers and abstracts from conferences. Information was obtained on the use of $\alpha_1$-PI in and outside Canada.

For the review of clinical and economic studies, two reviewers independently selected relevant articles using previously defined selection criteria. The Jadad scale and adequacy of allocation concealment were used to assess the quality of the included randomized controlled trials (RCTs). The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included cohort studies. Two reviewers independently extracted data. Meta-analysis was to be performed if data were suitable. Only a narrative synthesis of data was undertaken because the data were unsuitable for pooling.
Summary of Findings

Two RCTs, four retrospective cohort studies, and eight case series were selected for the clinical review. One head-to-head randomized trial did not have a non-active treatment arm. As a result, it was excluded from the primary analysis. The other RCT that compared $\alpha_1$-PI with placebo obtained a high quality score (4 of 5), but the concealment of allocation could not be determined. Three of four cohort studies obtained high quality assessment scores for patient selection, between-group comparability, and outcome assessment. Five economic evaluations were selected for the economic review. The overall quality of two cost analyses was poor. The study with the highest quality incorporated the impact of quality of life, and the incremental cost of augmentation therapy during the patients’ lifetime.

In the clinical review, the RCT did not provide convincing evidence on the effect of $\alpha_1$-PI in slowing the progression of lung function impairment. Computed tomography (CT) scans showed less lung tissue loss annually in the $\alpha_1$-PI group, but the difference did not reach statistical significance when the treatment and control groups were compared. In the RCT, there was no significant difference noted in adverse events (AEs) when the placebo and $\alpha_1$-PI groups were compared. Retrospective cohort studies showed that treatment with $\alpha_1$-PI, relative to no treatment, was associated with slower rates of decline of lung function, fewer lung infections, and prolonged survival, especially for those with moderate airflow obstruction. Commonly reported AEs were headache, allergic reaction, fatigue, or fever. Severe AEs that were associated with $\alpha_1$-PI were dyspnea, worsening of congestive heart failure, or severe allergic reactions. These have been reported in 1% of the study population.

The mean annual cost of augmentation therapy in three cost-effectiveness studies ranges between US$43,350 and US$60,268. This is close to the reported mean annual cost of augmentation therapy in Canada of about C$68,631. The incremental cost-effectiveness ratio (ICER) for lifetime treatment is reported to be US$333,449 per quality-adjusted life-year (QALY) gained (2004 values).

Prolastin is mainly distributed through pharmacies in Canada; patients also receive Prolastin through hospital blood banks. Many provinces do not cover the expenses of patients with AAT deficiency who need treatment with Prolastin. The product is marketed in several European countries where funding is provided. The funding details are unknown.

Conclusions and Implications

Augmentation therapy has not demonstrated a therapeutic advantage compared to normal care, in RCTs. In non-randomized trials, $\alpha_1$-PI is associated with outcomes that demonstrate a therapeutic benefit in patients with severe AAT deficiency and moderate airflow obstruction. The benefits include slower progression of lung function impairment, reduced rates of upper respiratory tract infections, and prolonged survival. Harm from severe AEs that are associated with treatment occurs in approximately 1% of patients. There have been no deaths or transmitted infections attributed to augmentation therapy. No evidence was found to evaluate $\alpha_1$-PI’s effectiveness for improving quality of life, improving activity limitation, reducing the use of oxygen and rescue medications, or other health outcomes.

No evidence was found to evaluate $\alpha_1$-PI’s effectiveness in patients with AAT deficiency and no lung function impairment.

In directly comparing the lifetime treatment strategy with no treatment, the ICER of US$333,449 per QALY is higher than the commonly used threshold value for the adoption of other treatments. While treatment with $\alpha_1$-PI may not be cost-effective according to conventional criteria, it is the only available form of augmentation therapy for patients with severe AAT deficiency.

Additional studies are needed to further evaluate augmentation therapy for its clinical effectiveness and cost-benefit in this setting. Randomized trials may be difficult because of the low disease prevalence. Achieving sufficient sample sizes would be a challenge. Moreover, because of the slow progression of the disease, long-term patient follow-up would be required.
ABBREVIATIONS

α₁-PI  α₁-proteinase inhibitor
AAT  α₁-antitrypsin
AEs  adverse events
AIDS  acquired immunodeficiency syndrome
CLYS  cost per life-year saved
COPD  chronic obstructive pulmonary disease
CRDQ  Chronic Respiratory Disease Questionnaire
CT  computed tomography
DEALE  declining exponential approximation of life expectancy
FEV₁  forced expiratory volume in one second
FVC  forced vital capacity
ICER  incremental cost-effectiveness ratio
ICLYS  incremental cost per life-years saved
ILYS  incremental life-years saved
LYS  life-years saved
NHLBI  National Heart, Lung, and Blood Institute
NOS  Newcastle-Ottawa Scale
QALY  quality-adjusted life year
QOL  quality of life
RCT  randomized controlled trial
SF-36  36-Item Short Form Health Survey
SGRQ  St. George’s Respiratory Questionnaire
URTI  upper respiratory tract infection
vCJ  variant Creutzfeldt-Jakob disease
1 INTRODUCTION

1.1 Review of Therapeutics

1.1.1 Disease prevalence and incidence

\( \alpha_1 \)-antitrypsin (AAT) deficiency was first described in 1963.\(^1\) Severe deficiency of this protein occurs as a result of the inheritance of two proteinase inhibitor deficiency alleles from the AAT gene located on chromosome 14.\(^2,3\) Pulmonary emphysema presenting as chronic obstructive pulmonary disease (COPD) is the most prevalent clinical presentation, and is the major cause of disability and death,\(^4\) with liver disease being the second most frequent clinical complication.\(^5,6\)

Approximately 100 genetic variants of AAT have been identified. The normal genetic phenotype is PI*MM. Approximately 2% to 3% of Caucasians are heterozygous (PI*MZ or PI*MS) and are not considered to be at a significantly increased risk for the development of COPD.\(^7\) The exact prevalence in adults of the homozygote PI*ZZ phenotype (AAT deficiency), which is typically associated clinically with significant disease, is unknown. The prevalence of AAT deficiency (PI*ZZ), which was obtained from screening studies, has been found to range from one in 1,600 newborns\(^8\) to one in 5,097 newborns.\(^9\) The gene frequency seems to be the highest in individuals of northern and western European descent.\(^10\) In adult patients with COPD, the PI*ZZ phenotype was found to have a prevalence of about 4.5%.\(^11\)

It is estimated that 5% of AAT-deficient individuals have been diagnosed.\(^12\) Based on an adult prevalence of one in 6,000, it has been estimated that AAT deficiency affects 5,000 Canadians.\(^7\)

1.1.2 Description of intervention

One formulation of purified \( \alpha_1 \)-proteinase inhibitor (\( \alpha_1 \)-PI) is available in Canada (Prolastin®, Talecris Biotherapeutics). It is indicated for “chronic replacement therapy of individuals having congenital deficiency of \( \alpha_1 \)-PI with clinically demonstrable panacinar emphysema.”\(^13\) This is administered as a once weekly intravenous infusion at a dose of 60 mg/kg. By following this dosing regimen, the biochemical indices of drug efficacy are met (i.e., serum levels exceed the protective threshold between doses). Alternative dosing regimens have been examined, including 120 mg/kg administered every two weeks, or 250 mg/kg administered every four weeks. The biweekly regimen does not ensure protective serum levels throughout the interval between doses. The regimen of once every four weeks produces safe levels for 25 of the 28-day interval between doses.\(^14\) This dosing regimen was only formally studied in nine patients.

1.1.3 Standards of therapy

The Canadian Thoracic Society recommends that all patients receive appropriate therapy to optimize the clinical manifestations of their COPD.\(^15\) It also recommends that augmentation therapy be reserved for AAT-deficient patients with impaired forced expiratory volume in one second (FEV\(_1\)), who have quit smoking and are on optimal medical therapy, but continue to show a rapid decline in lung function.\(^7\)

The American Thoracic Society and the European Respiratory Society recommend augmentation therapy for individuals with established airflow obstruction from AAT deficiency. They state that augmentation therapy is not recommended for individuals without emphysema, and benefits in individuals with severe (FEV\(_1\)<35% predicted) or mild (FEV\(_1\)>50 to 60% predicted) airflow obstruction are less clear. They also recommend optimal management of the associated obstructive lung disease.\(^11\)

Recommendations from these three specialty societies are not consistently followed, perhaps because of the medication costs associated with augmentation therapy in Canada.

1.1.4 Identifying appropriate patients

Only patients with known genotypes that place them at risk for early emphysema should receive augmentation therapy. As a result, the identification of appropriate individuals requires the use of specific screening studies. AAT levels can be measured in the serum, and specific phenotypes can be defined by isoelectric focusing. When needed, specific genotypes can be analyzed by using a polymerase chain reaction for specific DNA sequences. Most
centres will have access to the testing needed to define individuals with AAT deficiency. A larger clinical barrier to identifying individuals who might receive augmentation therapy is deciding whom to test. The Canadian Thoracic Society’s recommendations suggest that COPD patients with the following be screened for AAT deficiency: early onset of disease; positive family history for AAT deficiency; and family history of disabling COPD occurring between ages 40 and 50 years old. The American Thoracic Society and the European Respiratory Society guidelines include more specific recommendations for screening (in decreasing likelihood of finding deficiency): confirmation of absent AAT peak on serum protein electrophoresis; early onset pulmonary emphysema; family members of known AAT-deficient patients; dyspnea and cough occurring in multiple family members in the same or different generations; liver disease of unknown cause; all subjects with chronic obstructive pulmonary disease; adults with bronchiectasis without evident etiology; patients with asthma whose spirometry fails to return to normal with therapy; and unexplained panniculitis and anti-proteinase-3 vasculitis.

The diagnosis of COPD, which is a prerequisite for many of the indications for screening, requires the measurement of persisting airflow obstruction using formal pulmonary function testing. Among 405 patients with a physician diagnosis of COPD, who were screened for concomitant heart failure, 61.2% actually had COPD according to standard, objective criteria. In this study, 33 patients had heart failure without evidence of COPD. As a result, it is likely that many patients with a presumptive diagnosis of COPD are misdiagnosed. This may limit the appropriate selection of patients for AAT-deficiency screening.

1.1.5 Potential for off-label use

There is little potential for the off-label use of Prolastin, based on clinical practice, specialty society guideline recommendations, and medication cost. An off-label use is possible for patients without lung function impairment.

The total dose administered or the dosing intervals may not follow accepted regimens. A review of the National Institutes of Health (NIH) registry data revealed variations in the dosing frequency, with two to three weeks being the most common dosing interval (43% of those receiving therapy). Physicians recommended augmentation therapy for ~10% of registry patients with FEV1>80%, consistent with the American Thoracic Society’s guidelines.

2 RESEARCH QUESTIONS

1. What is the evidence of clinical effectiveness (improved health outcomes, improved intermediate outcomes, and reduced harm) of human α1-PI compared with no human α1-PI in patients with AAT deficiency, and a diagnosis of COPD or no diagnosis of COPD?
2. What is the evidence of cost-effectiveness of using human α1-PI compared with no human α1-PI in patients with AAT deficiency?
3. What is the status of α1-PI in publicly funded drug plans in Canada?
4. In similar health jurisdictions outside Canada (US, New Zealand, Australia, and Europe), how is α1-PI funded?

The analytic frameworks for research question 1 are presented in Figures 1 and 2. The purpose of this approach, adopted from the third US Preventive Services Task Force, is to present in a graphical format, the questions that need to be answered during the literature review. The specific questions are depicted by links between interventions and outcomes. These links serve the dual purpose of identifying questions to help structure the literature review, and providing an evidence map after the review for identifying gaps and weaknesses in the evidence.
**Key Questions**

1. What are the health outcomes (reduced mortality or severe morbidity, reduced hospital stay, lung transplantations, improved function, reduced exacerbations, upper respiratory tract infections, use of rescue steroids, antibiotics, oxygen, quality of life) associated with human $\alpha_1$-PI use in patients with AAT deficiency and a COPD diagnosis?

2. What are the intermediate outcomes (computed tomographic scan of disease, spirometric, lung volumetric, or biochemical) associated with human $\alpha_1$-PI use in patients with AAT deficiency and a COPD diagnosis?

3. What harm (incidence of blood product disease, local and systemic allergic reactions) is associated with human $\alpha_1$-PI use in patients with AAT deficiency and a COPD diagnosis?
Figure 2: Analytic Frameworks (Prevention)

Key Questions

1. What are the health outcomes (reduced mortality or severe morbidity, reduced hospital stay, lung transplantsations, improved function, reduced exacerbations, upper respiratory tract infections, use of rescue steroids, antibiotics, oxygen, quality of life) associated with human α₁-PI use in patients with AAT deficiency and without a COPD diagnosis?

2. What are the intermediate outcomes (CT scan of disease, spirometric, lung volumetric, or biochemical and diagnoses of COPD) associated with human α₁-PI use in patients with AAT deficiency and without a COPD diagnosis?

3. What harm (incidence of blood product disease, local and systemic allergic reactions) is associated with human α₁-PI use in patients with AAT deficiency, but without a COPD diagnosis?
3 REVIEW METHODS

3.1 Overview of Process

To ensure the scientific rigour and relevance of the work, the research team is charged with developing analytic frameworks, key research questions, and selection criteria for admissible evidence.

The HTIS staff use these tools to create a literature search strategy that best captures the appropriate evidence (Appendix 1). They use the criteria for admissible evidence (explicit inclusion and exclusion criteria) to select papers that provide information to help answer the key questions; and they abstract key data from the selected papers. The quality (internal and external validity) of the evidence in each paper, and the coherence of the evidence for each key question is assessed and used to interpret results.

3.2 Selection Criteria

3.2.1 Clinical review

The HTIS staff write a draft report of their work and findings. A meeting is held to discuss the results, create a discussion section, and discuss the implications for decision makers, based on a structured discussion approach.18 The final report is then drafted and circulated to members of the team for approval. The final report provides information on what the team found and what they did not find, including areas where it is necessary to extrapolate from one situation to another.

All summaries are subjected to internal editorial review, and rigorous external peer review by independent clinical experts, assessment experts, or representatives of professional organizations and societies. The comments are assembled by an HTIS director or manager, and the authors are required to respond.

<table>
<thead>
<tr>
<th>Types of publications</th>
<th>published or unpublished reports in English</th>
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<tbody>
<tr>
<td>Types of trials</td>
<td>any design, including randomized controlled trials (RCTs) (parallel; blinded or unblinded), cohort studies, case-control studies, and case series; case reports and review articles are excluded</td>
</tr>
<tr>
<td>Types of interventions</td>
<td>human fractionated α1-PI at any dose; patients may also be on any standard therapy for COPD</td>
</tr>
<tr>
<td>Appropriate comparators</td>
<td>no therapy or placebo; patients may also be on any standard therapy for COPD</td>
</tr>
<tr>
<td>Types of patients</td>
<td>two groups are analyzed separately</td>
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<tr>
<td></td>
<td>• patients diagnosed with demonstrated mild, moderate, or severe COPD [as diagnosed by Global Initiative for Chronic Obstructive Lung Disease (GOLD),19 Canadian Thoracic Society (CTS),15 American Thoracic Society (ATS),20 or acceptable equivalent], and have diagnoses of AAT deficiency</td>
</tr>
<tr>
<td></td>
<td>• patients with no COPD, and who have diagnoses of AAT deficiency</td>
</tr>
<tr>
<td>Types of outcome measures</td>
<td>• health outcomes: death; severe or life-threatening events; exacerbations; URTI during treatment; hospitalizations during treatment; use of rescue steroids, antibiotics, and oxygen; improved functionality as measured by a validated scale; quality of life, measured by SGRQ, CRDQ, or SF-36; and lung transplantation surgery</td>
</tr>
<tr>
<td></td>
<td>• intermediate outcomes: lung function including FEV1, FVC, and FEV1/FVC ratio; biochemical tests such as serum concentration of AAT; diagnosis of COPD (for those without this diagnosis at the start of treatment with Prolastin), time to diagnosis, or percentage of COPD diagnosis between treatment arms</td>
</tr>
<tr>
<td></td>
<td>• harm outcomes: blood product disease (e.g., vCJ, AIDS, hepatitis B); and local or systemic allergic reactions</td>
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URTI = upper respiratory tract infection, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, SGRQ = St. George’s Respiratory Questionnaire, CRDQ = Chronic Respiratory Disease Questionnaire, SF-36 = 36-Item Short Form Health Survey, COPD = chronic obstructive pulmonary disease; vCJ = variant Creutzfeldt-Jakob disease, AIDS = acquired immunodeficiency syndrome.
Two reviewers (SC and RB) independently reviewed citations and abstracts, and applied the selection criteria. If the citation title or abstract met all the criteria, or if there was uncertainty or disagreement, the paper was obtained in full text. Two reviewers (SC and RB) then independently applied the same selection criteria to the papers obtained in full text, to make the final selection of the relevant articles to be included in the review. Disagreements were resolved through consensus or a third party.

### 3.2.2 Economic review

- **Study design:** full economic evaluation such as cost-effectiveness analysis, cost-utility analysis or only costing analysis
- **Population:** patients with AAT deficiency
- **Intervention:** human \(\alpha_1\)-PI (Prolastin)
- **Comparator:** no treatment
- **Costs and outcomes:** reported as aggregated estimates of cost-effectiveness, disaggregated estimate of incremental cost, or effectiveness from no intervention to adopting intervention, such as mean weekly, monthly, annual, and lifetime direct medical costs of augmentation therapy, and cost per life-year saved (CLYS); health-related outcomes such as life-years saved (LYS) and quality-adjusted life-years (QALY); incremental cost-effectiveness ratio (ICER); and incremental cost per life-year saved (ICLYS).

Two reviewers (FF and SC) independently reviewed citations and abstracts, and applied the selection criteria. If the citation title or abstract met all the criteria, or if there was uncertainty or disagreement, the paper was obtained in full text. Two reviewers (FF and SC) then independently applied selection criteria to the papers obtained in full text, to make the final selection of the relevant articles to be included in the review. Disagreements were resolved through consensus or a third party.

### 3.2.3 Additional information

The Canadian Agency for Drugs and Technologies in Health (CADTH) contacted representatives from Canadian health jurisdictions (members of CADTH’s Advisory Committee on Pharmaceuticals) to obtain information regarding the current status of \(\alpha_1\)-PI in publicly funded drug plans in Canada.

The survey questions were:
- Are patients who are prescribed \(\alpha_1\)-PI for the treatment of AAT deficiency obtaining the product from their local pharmacy, or do they need to go to another provider (e.g., local hospital blood bank, local health district)?
- Is \(\alpha_1\)-PI covered under your respective jurisdiction’s drug program? If so, are all patients covered; or are a portion of patients covered, based on restrictions such as age grouping or severity of the disease?
- If \(\alpha_1\)-PI is covered under your jurisdiction’s drug program, what is the approximate number of patients covered? Is there any deductible to pay, or are patients fully reimbursed?

A request for information was also sent to an e-mail network of International Network of Agencies for Health Technology Assessment (INAHTA) members. Several databases were searched for additional information.

### 3.3 Literature Search

Published literature was obtained by cross-searching BIOSIS Previews®, EMBASE®, and MEDLINE® databases on the DIALOG® search system. Retrieval was limited to the publication years 1990 to 2005 (September). Regular alerts were established on all databases and information received through alerts is current to December 2, 2005. Parallel searches were performed on PubMed and the Cochrane Library databases. All results were limited to English language articles. The manufacturer was also asked to supply information.

The web sites of regulatory agencies, and health technology assessment and related agencies were also searched, as were specialized databases such as those of the University of York Centre for Reviews and Dissemination. The Google™ and Yahoo™ search engines were used to search for information on the Internet. These searches were supplemented by hand searching the bibliographies of selected papers and abstracts from conferences including the American Thoracic Society International Conference 2001 to 2005, and the European Respiratory Society Annual Congress 2001 to 2004.

Appendix 1 includes more details on search strategies.
3.4 Data Analysis

3.4.1 Clinical review

a) Data extraction

Two reviewers (SC and RB) independently abstracted data on participants’ characteristics, intervention details, and outcome measures from the included studies; and created the evidence tables. The same two reviewers also independently checked the accuracy of the data included in the evidence tables.

b) Assessment of quality

Methodological quality was assessed to determine the extent to which each study’s design and reporting addressed bias in the comparison of interventions. For RCTs, we used the Jadad scale to assess the appropriateness of randomization and double-blinding, and how withdrawals and dropouts were counted. The adequacy of concealment of allocation to treatment was also judged. The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of non-randomized comparative studies, based on the selection of the cohorts, the comparability between cohorts, and the adequacy of the ascertainment of the study’s outcomes. Disagreements were resolved through discussion until consensus was reached.

c) Statistical analysis

The statistical synthesis of data extracted from RCTs was planned if the authors judged meta-analysis to be appropriate; otherwise, the results of each study were to be presented in tabular form. After review of included studies, the statistical pooling of evidence from RCTs was judged to be inappropriate because of differences across study design and follow-up (i.e., clinical heterogeneity). All data (RCT and non-randomized trials) are presented descriptively.

3.4.2 Economic review

Because the included studies varied significantly in terms of study design, data collection, and analysis, no effort was made to pool the results quantitatively. Instead, the results of each included study are presented in tabular form. All costs have been adjusted according to the Consumer Price Index for all Urban Consumers in US dollars (2004).

4 FINDINGS

4.1 Findings from Literature

A total of 561 abstracts were initially identified. After following the selection process, two RCTs, four retrospective cohort studies, and eight case series were included for the clinical review. The reasons for excluding or including clinical and economic articles that were initially considered are described in Appendix 2.

Figure 3 illustrates the selection of clinical trials and economic evaluations.

4.2 Clinical Trial Data

One study was exclusively conducted in Canada. Most of the studies’ patients were from Europe or the US. All the trials assessed the clinical effectiveness of α1-PI for patients with AAT deficiency and various levels of airflow obstruction. One RCT (the head-to-head trial), one cohort study, and four case series indicated that they were wholly or partially funded by the drug manufacturer. The head-to-head RCT trial examined the biochemical equivalence between two human plasma-derived AATs. It did not have a non-active treatment arm or a placebo group, so it could not answer the research questions with respect to the clinical effectiveness of α1-PI. Nonetheless, because this RCT provided information on other outcomes such as AEs, it was included in the clinical review.

4.2.1 Quality assessment

The RCT by Dirksen et al. obtained a high score (4 of 5), but the concealment of allocation in this study could not be determined (i.e., was unclear). The quality of the included cohort studies was evaluated by using the NOS. Three of the four cohort studies had a higher score with respect to patient selection, comparability between groups, and outcome assessment.

4.2.2 Clinical effectiveness

The details of studies that evaluated the clinical effectiveness of α1-PI are provided in Table 1. The AEs (including serious AEs) that were reported in the included studies are listed in Table 2.
Figure 3: QUOROM flowchart

561 articles were identified from literature search; 28 reports were retrieved for detailed evaluation.

9 reports excluded:
- inappropriate intervention (6)
- inappropriate patient population (1)
- insufficient data (2)

19 relevant reports for inclusion in systematic review
- clinical (14): 2 RCTs, 4 cohort studies, 8 case series
- economic (5): 1 cost-utility and cost-effectiveness analysis, 2 cost-effectiveness analyses, 2 cost analyses
## Table 1: Clinical effectiveness of treatment with α₁-PI

<table>
<thead>
<tr>
<th>Included Studies</th>
<th>Design</th>
<th>Quality*</th>
<th>Participants' Characteristics</th>
<th>Intervention and Comparator</th>
<th>Outcome Measures and Results</th>
<th>Funding Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dirksen et al.²⁶</td>
<td>RCT</td>
<td>4 out of 5 (Jadad); unclear concealment</td>
<td>26 Danish and 30 Dutch ex-smokers, with moderate to severe emphysema; mean age 50.4±1.64 years for Danish pts, 45.1±1.17 for Dutch pts; FEV₁ 1,570/mL and 49.4±2.75% pred for Danish pts, 1,660/mL and 47.1±2.58% pred; 14 males and 12 females in Denmark, 20 males and 10 females in the Netherlands; 2 dropouts (both Dutch, resumed smoking); pts from AAT registries</td>
<td>tx=α₁-PI infusion every 4 weeks, 250 mg/kg; control=albumin infusion every 4 weeks, 625 mg/kg; tx duration ≥3 years</td>
<td>patient-administered serial spirometry at home (mL/year, mean±SE): tx=26.5±15.1, control=25.2±22.0, p=0.96; decline of FEV₁ measured at respiratory laboratory (mL/year, mean±SE): tx=78.9±12.0, control=59.1±11.9, p=0.25; 15th percentile point of lung density distribution of whole lung by CT (g/L): tx=−1.50±0.41, control=−2.57±0.41, p=0.07; mean levels of serum AAT at 28 days after last infusion (μM): tx=8.8, control=6.2, p&lt;0.001</td>
<td>non-industry</td>
</tr>
<tr>
<td>Seersholm et al.²⁷</td>
<td>cohort study, R</td>
<td>selection: 3 of 4; comparability: 2 of 2; outcome: 1 of 3 (NOS)</td>
<td>tx=198 German pts, mean age 46±8 years, 142 males, 56 females, ex-smokers (abstained for ≥3 months); initial FEV₁(% pred) 37±14% (patients from WATL database); non-tx=97 Danish pts, mean age 45±10 years, 55 males, 42 females, ex-smokers (abstained for ≥3 months), initial FEV₁(% pred) 42±10% (patients from Danish α₁-Antitrypsin Deficiency Register)</td>
<td>tx=weekly Prolastin, 60 mg/kg, duration ≥1 year, follow-up 3.2±1.6 years; non-tx=follow-up 5.8±3.4 years</td>
<td>decline of FEV₁ (mL/year, mean±SD) among German pts 53.0±37.6 overall, 24.2±23.6 for initial FEV₁(% pred) &lt;30%, 61.8±25.3 for initial FEV₁(% pred) 30% to 65%, 162.0±28.7 for initial FEV₁(% pred) &gt;65%; among Danish pts 74.5±59.6 overall, p=0.02; 30.9±36.3 for initial FEV₁(% pred) &lt;30%, p=0.6; 82.8±49.3 for initial FEV₁(% pred) 30% to 65%, p=0.04; 140.0±83.2 for initial FEV₁(% pred) &gt;65%, p=0.7</td>
<td>Bayer AG</td>
</tr>
<tr>
<td>Chapman et al.²⁸</td>
<td>cohort study, R</td>
<td>selection: 3 of 4; comparability: 2 of 2; outcome: 2 of 3 (NOS)</td>
<td>63 pts, 67% male, 33%, female. FEV₁(% pred) ≥50%=28%, FEV₁(% pred) 30% to 49%=48%, FEV₁(% pred) &lt;30%=24%; tx=21 pts, mean age 50.1±10.1 years; matched control (age, sex, and smoking)=42 pts, mean age 49.3±11.5 years, FEV₁(% pred) ≥50%=41%, FEV₁(% pred) 30% to 49%=33%, FEV₁(% pred) &lt;30%=26% (patients from Canadian AIR Registry)</td>
<td>dosage not indicated, tx duration=4.4 years, median observation period was 5.6 years</td>
<td>decline in FEV₁ (mL/year, 95% CI), tx=29.9, control group=63.6 (40.3 to 86.9), difference=33.7 (6.2 to 61.3), p=0.019</td>
<td>non-industry</td>
</tr>
</tbody>
</table>
## Table 1: Clinical effectiveness of treatment with α₁-Pi

<table>
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<tr>
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<th>Design</th>
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<th>Participants’ Characteristics</th>
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<th>Funding Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieberman²⁹ cohort study, R</td>
<td>selection: 3 of 4;</td>
<td>tx=96 pts receiving Prolastin, 50 men (all ex-smokers, median age 50 years), 46 women (43 ex-smokers, 3 non-smokers, median age 53 years), 89 pts used for data analysis; control group 47 pts, 12 non-smokers, 24 men (median age 55 years), 23 women (median age 45 years); significant difference between numbers of non-smokers in the 2 groups</td>
<td>various dose frequencies, total dose of Prolastin had been adjusted accordingly to equal 60 mg/kg as weekly dose</td>
<td>number of lung infections per year: significant difference found between pre-tx and during-tx, ( p \leq 0.001 ); significant difference found between tx (after therapy) and control group, ( p \leq 0.001 ); no significant difference found between tx (before therapy) and control group</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>AATD Registry Study Group³⁰</td>
<td>selection: 4 of 4;</td>
<td>total pts=1,129, 1,048 pts used for survival analysis, 927 pts used for FEV₁; decline analysis; 30% never, 42% always, and 28% partly received Prolastin; mean age 46±11 years, 55% male, 71% ex-smokers, 21.4% non-smokers, 8.1% current smokers, baseline FEV₁(% pred) 49±30%, baseline FEV₁ 1,748 mL; excluded 202 pts with &lt;2 FEV₁ readings, this group had more severe airflow obstruction at baseline; pts from NHLBI Registry.</td>
<td>dosing frequency varied (inter- and intra-variation); mean length of follow-up (only included survivors) 57±17 months</td>
<td>mortality overall: pts receiving Prolastin versus those not receiving Prolastin (adjusted for gender and other significant predictors) RR=0.64, ( p=0.02 ); initial FEV₁(% pred) 35% to 49%, lower for pts sometimes or always receiving Prolastin compared with those never receiving Prolastin RR=0.21, ( p \leq 0.001 ); initial FEV₁(% pred) ≥50% or &lt;35%, no significant different between groups RR=0.75, ( p=0.64 ); decline in FEV₁, overall: pts receiving Prolastin did not significantly differ from those not receiving Prolastin, mean difference 4 mL/year, ( p=0.40 ); mean FEV₁(% pred) of 35% to 49%, slower rate of decline observed for pts receiving Prolastin than for those not receiving Prolastin, mean difference 27 mL/year, ( p=0.03 )</td>
<td>non-industry</td>
<td></td>
</tr>
</tbody>
</table>

*Quality of RCT assessed with Jadad scale and adequacy of allocation concealment; quality of cohort study assessed with NOS; WATL=Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen; NHLBI=National Heart, Lung, and Blood Institute; tx=treatment; SE=standard error; R=retrospective; SD=standard deviation; pt=patient; NOS=Newcastle-Ottawa Scale; RR=relative risk; P=prospective; IV=intravenous; pred=predicted; NR=not reported.

**Human α₁-Proteinase Inhibitor for Patients with α₁-Antitrypsin Deficiency**
### Table 2: Adverse events and serious adverse events reported in included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Adverse Events</th>
<th>Serious Adverse Events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoller et al. 25</td>
<td>RCT</td>
<td>period of study: 10 wks; 3 pts with AEs among 14 pts on Prolastin; 5 pts with AEs among 14 pts on Respitin; description of AEs not provided</td>
<td>0 pt with SAE out of 14 pts on Prolastin</td>
</tr>
<tr>
<td>Dirksen et al. 26</td>
<td>RCT</td>
<td>period of study: 3 to 5 yrs; 0 pts with AEs among 26 pts on tx; 0 pts with AEs among 30 pts on placebo</td>
<td>not reported</td>
</tr>
<tr>
<td>Lieberman29</td>
<td>cohort study</td>
<td>period of observation: 1 to 10 yrs; 0 pts with AEs among 89 pts on tx; 0 pts with AEs among 47 pts not on tx</td>
<td>1 pt with SAE among 89 pts on tx; 2 pts with SAE among 47 pts not on tx, all were allergic reactions</td>
</tr>
<tr>
<td>Kropp et al.32</td>
<td>case series</td>
<td>period of observation: 24 hours; 4 pts with AEs among 18 pts (15 pts on IV tx and 3 pts on inhaled tx); headache (n=1); increased coughing (n=1); tickling of throat (n=1); sore throat (n=1)</td>
<td>not reported</td>
</tr>
<tr>
<td>Wencker et al.33</td>
<td>case series</td>
<td>period of observation: 1 to 6 yrs; 65 pts with AEs among 443 pts; 124 AEs among 443 pts, e.g. fevers and chills, urticaria, nausea and vomiting, fatigue, dyspnea; discontinuation due to AEs=3 pts</td>
<td>5 pts with SAEs among 443 pts; anaphylactic reactions (n=4); worsening of CHF and respiratory failure (n=1); 59 deaths among 443 pts due to underlying pulmonary disease</td>
</tr>
<tr>
<td>Barker, et al.34</td>
<td>case series</td>
<td>period of observation: 20 wks; 21 pts with AEs among 23 pts; 31 AEs among 23 pts, respiratory problems (11 AEs); headache (10 AEs); fatigue (9 AEs); chest tightness, muscle soreness, joint pain, and increased shortness of breath at every infusion (1 AE)</td>
<td>0 pt with SAE among 23 pts; 1 death among 23 pts due to acute bronchopneumonia</td>
</tr>
<tr>
<td>Schwaiblmair et al.35</td>
<td>case series</td>
<td>period of observation: 3 yrs; 1 pt with AE among 20 pts; low-grade fever and exanthema (n=1)</td>
<td>0 pt with SAE among 20 pts; 1 death among 20 pts (cause of death not provided)</td>
</tr>
<tr>
<td>Stoller et al.37</td>
<td>case series</td>
<td>period of observation: 3.5 to 7 yrs; 174 pts with AEs among 747 pts; 270 AEs among 747 pts, e.g. headache; dizziness; nausea; discontinuation due to AEs=3 pts</td>
<td>63 SAEs among 747 pts; dyspnea and shortness of breath; wheezing; hypotension</td>
</tr>
<tr>
<td>Barker et al.37</td>
<td>case series</td>
<td>period of observation: 12 to 48 mos; 4 pts with AEs among 14 pts; 10 AEs among 14 pts, back pain (2 AEs); headache (4 AEs); increased shortness of breath (4 AEs)</td>
<td>2 pts with SAEs among 14 pts; hospitalization due to hypotension and respiratory distress (n=1); unknown (n=1); 1 death among 14 pts due to respiratory failure</td>
</tr>
</tbody>
</table>

AEs=adverse events; SAEs=serious adverse events; pts=patients; tx=treatment; CHF=congestive heart failure; wks=weeks; yrs=years; mos=months.

*The World Health Organization defines serious AE as a medical occurrence that at any dose is life-threatening or results in death; requires inpatient hospitalization or prolongation of existing hospitalization; or results in persistent or significant disability or incapacity.38

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*Human α1-Proteinase Inhibitor for Patients with α1-Antitrypsin Deficiency* 11
In the RCT by Dirksen et al., 56 ex-smokers with moderate to severe emphysema were enrolled. Patients were randomized to receive α1-PI or placebo (albumin) in a double-blind approach. Patients were instructed on how to use spirometry at home, and they were required to visit the respiratory laboratory for lung function tests. Neither method showed a statistically significant effect of α1-PI augmentation on preventing the continuous decline of lung function in the study population, as compared with placebo. CT scans showed a trend toward α1-PI inhibiting annual lung loss, but this did not reach statistical significance (p=0.07). Patients in the treatment group had higher mean levels of serum AAT 28 days after the last infusion, compared with those in the control group (p<0.001). AEs were not observed in this trial.

The results from retrospective cohort studies implied that the augmentation of α1-PI was associated with slower rates of decline of lung function, or fewer lung infections, especially for the group with moderate emphysema, as compared with the patients who did not receive Prolastin treatment. Patients’ survival was assessed in a large cohort study with 1,129 participants, 1,048 of whom were considered in the survival analysis. It showed that after adjusting for confounders such as age, initial FEV1, smoking status, and gender, treatment with α1-PI was associated with lower mortality rates than no treatment [RR=0.64, 95% CI (0.43, 0.94), p=0.02]; this effect was greater among patients with moderate airflow obstruction of FEV1 35% to 49% of predicted [RR=0.21, 95% CI (0.09, 0.50), p<0.001].

Eight case series (Appendix 3) were included in our review, to supplement information about the benefit and harm derived from the comparative studies. They also reported lung function, and levels of serum AAT. In one small trial with 23 participants who received biweekly treatments, none of the patients maintained an effective serum AAT level in the second week after the infusion. Commonly reported AEs were headache, allergic reaction, fatigue, or fever (Table 2). Symptoms were mild to moderate in most cases. Severe AEs such as dyspnea, worsening of congestive heart failure, or severe allergic reactions were also reported. In the case series by Wencker et al., out of a total of 443 patients, 65 experienced ≥1 AEs for a total of 124 AEs. Five patients (1.1%) had a severe AE. In a case series of 747 out of 1,129 National Heart, Lung, and Blood Institute (NHLBI) registry enrollees receiving augmentation therapy, 63 severe AEs were reported after a follow-up of >3.5 years. There have been no deaths or transmitted infections attributed to augmentation therapy.

### 4.3 Economic Data

Details of the economic studies are presented in Table 3. All five economic evaluations of α1-PI studies occurred in the US (three cost-effectiveness studies, and two cost analyses). No such studies have been conducted in Canada. The interpretation and comparison of the five studies’ results are difficult, because they were based on a variety of assumptions, and on costs and measures of effectiveness from different sources with unclear scopes.

In two cost-effectiveness studies, Hay and Robin, and Atkins and O’Malley reported that although it is expensive, augmentation therapy is as cost-effective as many currently used treatments. Hay and Robin adopted the efficacy of augmentation therapy from Larsson’s study, and used a lower mean annual cost of therapy (US$43,350, 2004 value) compared with the other two cost-effectiveness studies. They also did not account for the differences in costs and quality of life (QOL) between health states. Their report was based on cost per life-year saved (CLYS) for different efficacy rates, and they reported that augmentation therapy would be cost-effective with an efficacy of ≥30%.
### Table 3: Economic evidence

<table>
<thead>
<tr>
<th>Authors, Type of Economic Evaluation</th>
<th>Participants’ Characteristics, Intervention, and Comparator</th>
<th>Health-related Outcome Indices: QALYs and LYS</th>
<th>Cost Indices: Mean Weekly, Monthly, Annual, Lifetime Direct Medical, and CLYS</th>
<th>Incremental Outcome Indices: ICER and ICLYS</th>
<th>Notes (e.g., discount rate, main results, issues, conclusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hay et al., cost-effectiveness analysis&lt;sup&gt;39&lt;/sup&gt;</td>
<td>246 Swedish adults with homozygous (PiZ) AAT deficiency and COPD; Prolastin administered once a week with a dosage of 60 mg/kg</td>
<td>life expectancy based on Larsson’s 1978 survival data; outcome efficacy is hypothetical; at a range of 10% to 90% efficacies, expected 5-year mortality differences are 0.015 to 0.139*</td>
<td>based on Medicare part B reimbursement rates; mean annual cost of augmentation therapy: US$30,000 (1990 value) and US$43,350 (2004 value); assuming 8-year median survival period before death; at 70% efficacy, CLYS ranged between US$28,000 and US$72,000 (1990 value); and US$40,460 and US$104,040 (2004 value); at 30% efficacy, CLYS ranged between US$50,000 and US$128,000 (1990 value), and US$72,250 and US$184,960 (2004 value)</td>
<td>NR</td>
<td>5% discount rate for future costs and benefits; with efficacy of ≥30%, therapy would be cost-effective&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alkins et al., cost-effectiveness analysis, NHLBI Registry&lt;sup&gt;40&lt;/sup&gt;</td>
<td>patients with severe COPD and AAT deficiency; weekly 1-hour therapy infusions of 60 mg/kg</td>
<td>life expectancy with DEALE assumes constant death rate; outcome efficacy based on NHLBI Registry data</td>
<td>based on Medicare part B reimbursement rates; costs calculation based on efficacy data from NHLBI Registry; mean annual cost of augmentation therapy US$52,000 annually (1998 value) and US$60,268 (2004 value) for 70 kg patient</td>
<td>at 10% to 70% efficacy, ICLYS between US$152.941 and US$7,330 (1998 values), and US$177.240 and US$8,495 (2004 values); at 55% efficacy, ICLYS for patients with FEV&lt;sub&gt;1&lt;/sub&gt;&lt;50% is US$13,971 (1998 value) and US$16,190 (2004 value)**</td>
<td>7% discount rate, using differences in cost and QOL between health states; lifelong augmentation therapy for individuals with severe AAT deficiency and severe COPD is cost-effective&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gildea et al., cost-effectiveness and cost-utility analysis&lt;sup&gt;41&lt;/sup&gt;</td>
<td>individual with severe AAT deficiency (NHLBI Registry); hypothetical 30,000 identical 46-year-old patients, 50% male with FEV&lt;sub&gt;1&lt;/sub&gt;, 49% using Monte Carlo simulation across five possible health states: FEV&lt;sub&gt;1&lt;/sub&gt;, 50% to 79%,</td>
<td>life expectancy based on Markov analytical model; outcome indices are QALY and ICER; estimated utility weights based on Health Utility Index for 14 respondents in each</td>
<td>based on average wholesale price and Medicare part B reimbursement; mean annual cost of augmentation therapy US$54,765 (2001 value) and US$58,434 (2004 value); cost of lifetime augmentation: US$895,243 (2001 value) and US$955,224 (2004 value); cost of augmentation for FEV&lt;sub&gt;1&lt;/sub&gt;&lt;35% estimated at US$511,930 (2001 value) and US$511,930 (2001 value)</td>
<td>health care system perspective, only direct costs; ICER for lifetime therapy per QALY gained estimated at US$312,511 (2001 value) and US$333,449 (2004 value)</td>
<td>0% to 7% discount rate; compared with other conventional health interventions, α&lt;sub&gt;1&lt;/sub&gt;-PI is less cost-effective; annual cost of α&lt;sub&gt;1&lt;/sub&gt;-PI needed to be reduced from US$58,434 to US$5,230 for lifetime therapy per QALY gained estimated at US$312,511 (2001 value) and US$333,449 (2004 value)</td>
</tr>
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<th>Notes (e.g., discount rate, main results, issues, conclusion)</th>
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<tr>
<td>Mullins et al., cost analysis&lt;sup&gt;42&lt;/sup&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; 35% to 49%, FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sub&gt;&lt;&lt;/sub&gt;35%, post lung transplantation, death; weekly 1-hour augmentation therapy infusions of 60 mg/kg</td>
<td>health state in model; QALY&lt;sub&gt;&gt;&lt;/sub&gt;7.19 for lifetime augmentation; QALY&lt;sub&gt;&lt;&lt;/sub&gt;4.62 for no augmentation; QALY&lt;sub&gt;&lt;&lt;/sub&gt;6.64 for augmentation until FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sub&gt;&lt;&lt;/sub&gt;35%</td>
<td>US$546,229 (2004 value); cost of no augmentation US$92,091 (2001 value) and US$98,261 (2004 value); cost of 1-hour infusion weekly, 4,200 mg of Prolastin sensitivity analyses: treat-life versus no treatment led to 9 LYS at cost of US$1.20 million (2001 value) and US$1.28 million (2004 value)</td>
<td>value); ICER for FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sub&gt;&lt;&lt;/sub&gt;35% and &gt;50% therapy per QALY gained is US$207,841 (2001 value) and US$221,690 (2004 value)</td>
<td>considered cost-effective</td>
</tr>
<tr>
<td>Mullins et al., cost analysis&lt;sup&gt;43&lt;/sup&gt;</td>
<td>based on survey from members of Alpha One Foundation Registry (NHLBI Registry), weekly or monthly administration depends on patient’s weight; weekly dosage of 60 mg/kg, infusion time of 1 hour; monthly infusion with dosage 250 mg/kg and infusion time of 4 hours</td>
<td>NR</td>
<td>Costs based on survey; estimated annual direct medical costs based on cost per unit of utilization×frequency of utilizations; mean annual cost of augmentation therapy US$32,606 to US$67,430 (1990 value) and US$47,116 to US$97,436 (2004 value)</td>
<td>NR</td>
<td>lack of costs by specific items of care (e.g., drugs and physician visits)</td>
</tr>
</tbody>
</table>

Cost data adjusted for Consumer Price Index for all urban consumers in 2004 US$ value. ¹Efficacy of therapy defined as change in survival rate. ²At 70% efficacy, $30,000 of therapy buys about a year of additional life expectancy. ³Because only 50,000 to 100,000 individuals in US are potentially treatable, screenings would add significantly to cost of intervention, even if Prolastin were highly efficacious. ⁴Medication cost if $105 per 500 mg α₁-PI, and a 70 kg patient would require nine 500 mg α₁-PI weekly. Five-year total cost would be about $260,000 ($52,000×5). Cost-effectiveness is calculated as $260,000/18.61 years=$13,971 per year of life saved. DEALE=declining exponential approximation of life expectancy; NR=not reported.
Alkins and O’Malley used an annual mean cost of augmentation therapy of about US$60,268 (2004 value).40 To estimate the efficacy, they used a simple model of Declining Exponential Approximation of Life Expectancy (DEALE), which can result in a biased estimate of effectiveness. The DEALE assumes a constant baseline mortality rate, which implies that the remaining lifetime is assumed to have an exponential distribution. This leads to assigning more weight to the underestimated early survival than to the overestimated late survival, and thus underestimates the new life expectancy due to the excess mortality.44

With the differences in cost and QOL between health states, they used the incremental cost per life-year saved (ICYLS as opposed to CLYS in Hay and Robin). The medication cost was US$105 per 500 mg $\alpha_1$-PI, and a 70 kg patient would need nine 500 mg doses of $\alpha_1$-PI weekly. The five-year total cost would be about US$260,000 (US$52,000×5). The cost-effectiveness was calculated as US$260,000/18.61 years=$13,971 annually of life saved (1998 value) and US$16,190 (2004 value). Although they assumed that augmentation therapy would be used for five years, the costs would be distributed during the entire expected benefit interval of 18 years (Alkins and O’Malley offer a detailed estimation). They concluded that lifelong augmentation therapy for individuals with severe AAT deficiency and severe COPD was cost-effective. For example, at an efficacy of 10% to 70%, an additional cost of US$152,941 to US$7,330 can buy an additional life-year (ICLYS).

The third cost-effectiveness study, conducted by Gildea et al.,41 used a Markov model to analyze the cost-effectiveness of different strategies of augmentation therapy. This study presented the aggregated and disaggregated form of costs, effectiveness, incremental costs, incremental effectiveness, and the incremental cost-effectiveness ratio of the lifetime and discontinued courses of augmentation therapy compared with no treatment. The mean annual cost of augmentation therapy in Gildea et al. was reported to be about US$58,434 (2004 value). The cost of lifetime $\alpha_1$-PI therapy was US$955,224 (2004 value). This produced 7.19 QALYs, compared with no augmentation therapy at a cost of US$98,261 and 4.62 QALYs. The incremental lifelong augmentation therapy cost for individuals with severe AAT deficiency and severe COPD was reported to be about US$856,963 (US$955,224 to US$98,261), and produced a mean incremental score of 2.57 (7.19 to 4.62) QALYs. In comparing directly the lifetime treatment strategy with no treatment, the ICER was estimated at about US$333,449 per QALY (US$856,963 per 2.57 QALY, in 2004 values). The incremental cost-effectiveness ratio (ICER) is reported as (cost of augmentation therapy−cost of no treatment)/(QALY of augmentation therapy−QALY of no treatment).

While the results from the first two cost-effectiveness studies (Hay and Robin, and Alkins and O’Malley) were sensitive to the efficacy and therapy costs assumptions, the results in Gildea et al. were not sensitive to the efficacy assumptions. Gildea et al. concluded that Prolastin is expensive and appears to be cost-effective only if its annual cost is reduced from US$58,434 to US$5,230 for the life-strategy to reach an ICER <US$50,000 (2004 value) per QALY gained.41 Even after changing the sensitivity analysis for all utilities or costs simultaneously, no strategy produced an ICER below the threshold value of US$100,000 per QALY. For example, the ICERs for smoking cessation interventions were reported to be about US$1,302 to US$5,337 per QALY;45 US$14,015 per QALY for the treatment of severe hypertension in men;46 US$19,650 per QALY for the treatment of type II diabetes;47 and US$57,285 per QALY for cholesterol reduction in patients with type II diabetes.48

Gildea et al., using QALYs as opposed to LYS and ILYS, which were used in the other two cost-effectiveness studies,39,40 incorporated the effects of treatment on the quality and quantity of life in estimating the cost-effectiveness of augmentation therapy. Their study includes the cost of therapy for COPD (medications, oxygen therapy, laboratory and diagnostic tests, clinic and emergency department visits, and hospitalizations) versus only augmentation therapy. Although the Markov model is useful to model treatment under a variety of conditions and to estimate the probability of outcome, some assumptions must be made to develop this model, which is not based directly on empirical data.

To compare a more accurate range of costs of augmentation therapy, two cost-analysis studies conducted by Mullins et al. in 2001 and 2003 were
included. Both were based on a survey from the NHLBI. Both studies had shortcomings according to conventional criteria. There is a lack of information about the scope of costs by specific items of care (such as drugs and physician visits) in the 2001 study, and the results from the 2003 study were based on a low response rate of 39% of potential respondents. The mean annual costs of augmentation therapy have been estimated to be in the range of US$32,539 to US$97,436 (2004 value).

Among the three cost-effectiveness analyses examined, the highest quality study was that by Gildea et al. In contrast to the other two cost-effectiveness studies, Gildea et al. incorporated the impact of QOL using the HUI-3 (Health Utility Index) and the incremental cost of augmentation therapy (on the basis of NHLBI Registry data) during the lifetime of the patients. None of the studies, however, incorporated AEs in estimating the cost-effectiveness analysis. This omission may result in an underestimation of the costs of treatment.

From the five studies, it is concluded that treatment with α₁-PI is expensive. The mean annual cost of augmentation therapy ranges between US$43,350 and US$60,268 (2004 value reported in three of five studies: Alkins and O’Malley, Gildea et al., and Mullins et al. in 2001). This is close to the reported C$68,631 (2004 value) mean annual costs of augmentation therapy in British Columbia. In 2004, BC PharmaCare covered Prolastin for 30 patients, for a total cost of C$2,058,918.26 (Ken Sudhues, BC Ministry of Health, Victoria: personal communication, 2005 Sep 20). (C$2,058,918.26/30 patients=C$68,631 per patient). The reported estimates of the previous cost-effectiveness studies of augmentation therapy with α₁-PI, depending on the therapy cost assumptions, ranged between US$40,460 and US$184,960 for the CLYS (Hay et al. 1991) and US$16,190 for the ICYLS (Alkins et al. 2000).

In comparing directly the lifetime treatment strategy with no treatment, the ICER of US$333,449 per QALY is higher than the commonly used willingness-to-pay threshold value for other treatments. Gildea et al. suggested that while augmentation therapy does not satisfy the conventional criteria for cost-effectiveness, continued use is recommended, because it is the only available therapy that is specifically used for severe AAT deficiency.

4.4 Other Findings

From Canada (Table 4), all nine provinces that are represented on CADTH’s Advisory Committee on Pharmaceuticals and the Non-Insured Health Benefits Program (NIHB) responded to our request for information on drug funding status. Prolastin is covered as a full benefit without restrictions by British Columbia’s drug plan. The Atlantic provinces and NIHB do not cover Prolastin under their drug programs. In Ontario, it may be covered through a Section 8 mechanism (special permission for reimbursement), and deductible requirements must be met (depends on income). In Manitoba, Prolastin is covered under an Exception Drug Status, and patients must meet deductible requirements. In Saskatchewan, it was de-listed from the formulary in 1992. In Canada, fewer than 40 patients are covered.

From outside Canada (Table 5), the product is marketed in several European countries where funding is provided. The specific funding details are unknown.

5 DISCUSSION

AAT deficiency predisposes individuals to the development of early onset emphysema and bronchiectasis. It is also associated with liver disease. Emphysema usually develops by the fifth to sixth decade in AAT-deficient patients, but appears as early as the fourth decade in smokers.

The aim of augmentation therapy is to restore the level of AAT in the human body, and prevent or slow the progress of emphysema. The therapy became available for prescription use in Canada in 1988.7,13 Commercially available α₁-PI formulations include Prolastin (Talecris Biotherapeutics, Clayton, NC), Aralast™ (Baxter, Deerfield, IL), and Zemaira™ (ZLB Behring, King of Prussia, PA). All are produced from pooled human plasma. The standard therapy requires weekly infusions of Prolastin at a dose of 60 mg/kg. Only Prolastin has received regulatory approval in Canada. This treatment is recommended for severe AAT-deficient patients with moderate airflow obstruction.
<table>
<thead>
<tr>
<th>ACP Member</th>
<th>Question 1: Pharmacy or other provider of Prolastin*</th>
<th>Question 2: Formulary status†</th>
<th>Question 3: Number of patients covered and whether there is a deductible‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta (AB) (Marlain Wong, Alberta Health, Edmonton; personal communication, 2007 Jan 17)</td>
<td>NR</td>
<td>not listed as a benefit</td>
<td>N/A</td>
</tr>
<tr>
<td>British Columbia (BC) (Ken Sudhuues, BC Ministry of Health, Victoria; personal communication, 2005 Sep 20)</td>
<td>pharmacy dispenses product to patient</td>
<td>Prolastin covered as full benefit by BC PharmaCare, with no restriction</td>
<td>31 patients covered as of September 6, 2005, at a cost of C$1,182,694.99, with deductibles based on patient’s income</td>
</tr>
<tr>
<td>Manitoba (MB) (Kathy McDonald, Manitoba Health, Winnipeg; personal communication, 2005 Sep 20)</td>
<td>pharmacy dispenses product to patient; drug must be infused outside hospital</td>
<td>Exception Drug Status program</td>
<td>&lt;5 patients covered under drug plan; patients must meet deductible before they get free product</td>
</tr>
<tr>
<td>New Brunswick (NB) (Leanne Jardine, Department of Health and Wellness, Fredericton; personal communication, 2005 Sep 14)</td>
<td>NR</td>
<td>not listed as a benefit of NB Prescription Drug Program, and requests for coverage are not considered</td>
<td>N/A</td>
</tr>
<tr>
<td>Newfoundland and Labrador (NL) (Patricia Clark, NL Prescription Drug Program, St. John’s; personal communication, 2005 Sep 13)</td>
<td>NR</td>
<td>not considered under any program</td>
<td>N/A</td>
</tr>
<tr>
<td>NIHB (Tuan Dang, Non-Insured Health Benefits Program, Ottawa; personal communication, 2005 Sep 13)</td>
<td>NR</td>
<td>does not cover blood products, clients referred to Canadian Blood Services</td>
<td>NR</td>
</tr>
<tr>
<td>Nova Scotia (NS) (Judy McPhee, Department of Health, Halifax; personal communication, 2005 Sep 13)</td>
<td>has not been prescribed</td>
<td>not covered under drug program</td>
<td>N/A</td>
</tr>
<tr>
<td>Ontario (ON) (Dr. Judith Glennie, Ontario Ministry of Health and Long Term Care, Toronto; personal communication, 2005 Sep 15)</td>
<td>pharmacy dispenses product to patient</td>
<td>not on formulary, requests considered through Section 8 mechanism (i.e., special permission for reimbursement)</td>
<td>&lt;5 recipients in 2004-2005; usual deductible rules applied (depends on income)</td>
</tr>
<tr>
<td>Prince Edward Island (PE) (Patrick Crawford, Provincial Pharmacy, Charlottetown; personal communication, 2005 Sep 13)</td>
<td>provided through local hospital blood bank</td>
<td>not covered by any PE drug programs, including special authorization</td>
<td>not covered</td>
</tr>
<tr>
<td>Saskatchewan (SK) (Gail Bradley, HEDP – Drug Plan Unit, Regina; personal communication, 2005 Sep 13)</td>
<td>NR</td>
<td>delisted in 1992 (&lt;5 patients grandfathered on drug at that time)</td>
<td>grandfathered patients on this drug receive it at no charge</td>
</tr>
</tbody>
</table>

*For patients who are prescribed Prolastin for treatment of AAT deficiency, are they obtaining product from their local pharmacy, or do they need to go to another provider (e.g., local CBS office, local hospital blood bank, local health district, other)? †Is Prolastin covered under your jurisdiction’s drug program? If so, what is Prolastin’s formulary status (general listing, restricted, other)? ‡If Prolastin is covered under your jurisdiction’s drug program, what is the approximate number of patients covered? Is there any deductible to pay or are patients totally reimbursed? N/A=not applicable; NR=not reported.
Augmentation therapy is expensive. In Canada, in 2001, about 60 adults with AAT deficiency and COPD were receiving Prolastin. In British Columbia, 31 patients have been covered as of September 6, 2005 at a cost of approximately C$1.2 million (Ken Sudhues, personal communication, 2005 Sep 20). The clinical and economic benefits from augmentation therapy remain uncertain. For this reason, CADTH systematically examined the available English-language medical and economic literature. In addition, a request was sent to publicly funded drug programs in Canada, and to an international health technology assessment network, to obtain an up-to-date picture of the use and coverage of \( \alpha_1 \)-PI in Canada and elsewhere.

From the medical literature, two RCTs, four retrospective cohort studies, and eight case series were identified for clinical review. One RCT could not be considered for the primary research question, because it involved a head-to-head...
comparison between Prolastin and another active treatment. The RCT that was included in the primary analysis obtained a high quality score as measured by the Jadad scale; three of four cohort studies obtained a high quality score, one obtained a low score, based on the NOS. For the economic review, five evaluations were identified: three were cost-effectiveness or cost-utility studies, and two were cost analyses. Among the five economic evaluations, the overall quality of the two cost analyses was poor, because of the lack of information about the scope of costs and a low response rate from potential respondents. Among the three cost-effectiveness analyses, the highest quality study was that by Gildea et al., as it incorporated the impact of QOL and the incremental cost of augmentation therapy.

The RCT by Dirksen et al. was included in the data analysis. It was labelled as a randomized double-blind controlled trial, but insufficient details about the study design were provided in the article to permit verification of the adequacy of concealment of patients’ allocation to treatment. An explicit conclusion cannot be drawn, because of small sample size, and near normal rates of lung function decline. This RCT failed to detect statistically significant differences between the treatment group and the placebo group. A possible reason for this would be that the small sample size (56 participants) hinders the detection of a meaningful difference (i.e., inadequate power). In the same study, the lung function was assessed by patient-administered serial spirometry at home, or by pulmonary function tests at respiratory laboratories. Technical factors may contribute to less valid results in home-based spirometry measurements. In addition, there was a surprising near normal rate of lung function decline of 25 mL for AAT-deficient patients receiving placebo. Patients who received augmentation therapy had a significantly higher serum AAT level 28 days after the infusion, implying that treatment can restore deficient AAT serum levels. The RCT by Stoller et al. was not placebo-controlled, and cannot be expected to provide evidence of clinical effectiveness compared to no therapy. Neither of the two RCTs evaluated health outcomes such as survival rates, QOL, or exacerbation frequency. Furthermore, the eligibility criteria for enrolment in both RCTs were inconsistent with those suggested by the Canadian Thoracic Society (CTS).

Guideline, in that only patients with moderate airflow obstruction (FEV1 values of 35% to 50% of predicted and a continuous rapid decline in FEV1>80 mL annually, given optimal medical therapy) are recommended to receive the augmentation therapy. The results from cohort studies show a trend of associated reductions in the rate of decline of FEV1 in patients who received augmentation therapy; the between-group differences were statistically significant for patients with moderate airflow obstruction. The cohort study with the highest quality score also examined the survival rates in the treatment group and the comparison group. It was shown that Prolastin therapy was associated with longer survival, especially for patients with moderate lung function impairment. Even though certain imbalances between groups, such as age, gender, or smoking status, were taken into account during data analysis, the results from retrospective cohort studies are generally viewed with caution, relative to those derived from an RCT, because of the inherent potential for bias.

Case series do not provide comparative evidence of effectiveness. They were included in this review to provide additional information, such as adverse effects (AEs) from treatment with α1-PI. Most of the AEs were mild to moderate; in larger studies, severe AEs were observed in ~1% of patients. No viral transmission of disease (e.g., vCJD) was observed. No death was attributed to the use of augmentation therapy in any study.

According to the clinical evidence examined in this report, augmentation therapy is associated with a slower rate of worsening of airflow obstruction in patients with AAT deficiency, a reduction in the frequency of upper respiratory tract infection, and decreased mortality. These effects are seen primarily in COPD patients with moderate obstruction.

Our findings are in line with those of a published meta-analysis of one RCT and four non-randomized trials of adult AAT-deficient patients that were conducted to examine the clinical effectiveness of augmentation therapy with α1-PI. It showed that patients receiving augmentation therapy had a slower rate of decline in lung function as measured by FEV1, particularly for those with a baseline FEV1 30% to 65% of predicted, as compared with...
the control group. However, the validity of the results from a meta-analysis of non-randomized controlled trials can be questioned, because of the unknown or unadjusted confounding factors that introduce bias. Another review article, a narrative of eight studies that evaluated the clinical effectiveness of α1-PI, drew similar conclusions to those in this report.

There are limitations to this review. Because of the nature of this report (a rapid response to the requestor), non-English language literature was excluded to save translation time. At the outset of this project, it was intended that the results would be statistically pooled. Because of the heterogeneity of the study populations and designs, however, the results of each included study were described only in narrative form. A few of the non-randomized studies examined health outcomes: one retrospective cohort study examined patients’ survival, another retrospective cohort study examined annual reduction in upper respiratory tract infection, and one case series reported the number of annual hospitalizations. Most of the included studies examined only intermediate outcomes, such as the decline in FEV1 and serum levels of AAT after the treatment. In non-randomized trials, significant differences existed between the treatment group and the comparison group for patients’ baseline characteristics, such as smoking status, and age and initial lung function. This makes the interpretation of the results more difficult, as it cannot be determined whether the observed differences in outcomes are due to the treatment or to the underlying differences between the treatment groups.

6 CONCLUSIONS AND IMPLICATIONS

Augmentation therapy has not demonstrated a therapeutic advantage compared to normal care, in RCTs. In non-randomized trials, α1-PI is associated with outcomes that suggest a therapeutic benefit in patients with severe AAT deficiency and moderate airflow obstruction. The benefits include slower progression of lung function impairment, reduced rates of upper respiratory tract infections, and prolonged survival. Harm from severe AEs that are associated with treatment occurs in approximately 1% of patients. There have been no deaths or transmitted infections attributed to augmentation therapy. No evidence was found to evaluate α1-PI’s effectiveness for improving quality of life, improving activity limitation, reducing the use of oxygen and rescue medications, or other health outcomes.

No evidence was found to evaluate α1-PI’s effectiveness in patients with AAT deficiency and no lung function impairment. Thus, the second part of our first research question could not be answered. This can be explained by the fact that the product is not indicated for patients without lung function impairment.

In directly comparing the lifetime treatment strategy with no treatment, the ICER is US$333,449 per QALY. While this would not be considered to be cost-effective according to conventional criteria, it is the only available form of augmentation therapy for patients with severe AAT deficiency.

Additional studies are needed to further evaluate augmentation therapy for its clinical effectiveness and cost-benefit in this setting. Randomized trials may be difficult because of the low disease prevalence. Moreover, because of the slow progression of the disease, long-term patient follow-up would be required. National registries may prove to be useful by providing data derived from the real world setting.

7 REFERENCES


Available:
http://www.chestjournal.org/cgi/reprint/124/3/826
(accepted 2007 Feb 6).


50. de Serres FJ. Alpha-1 antitrypsin deficiency is not a rare disease but a disease that is rarely diagnosed. Environ Health Perspect 2003;111(16):1851-4.


http://erj.ersjournals.com/cgi/reprint/7/11/1985
(accessed 2005 Sep 22).


http://www.chestjournal.org/cgi/reprint/127/4/1196
(accessed 2007 Feb 6).

APPENDICES
Available from CADTH’s web site
www.cadth.ca