

White Paper
Cystic Fibrosis:
Pulmonary Aspects of the Disease



Table of Contents

1. Introduction.....	3
2. Treatment of Cystic Fibrosis.....	3
3. Treatment of Pulmonary Exacerbations	6
4. Pulmonary Complications	7
5. Lung Transplantation	7
6. Conclusions.....	7
7. About the Author.....	8
8. References	8
9. About CROMSOURCE	9

1. Introduction

Cystic fibrosis (CF) is a genetic disease which is usually caused by the absence, dysfunction or reduced number of the multifunctional CF transmembrane regulator (CFTR) protein.. Recently new therapy approaches such as ivacaftor have emerged which target the cause of the condition itself. This white paper focusses only on the current treatment of pulmonary complications of CF.

Cystic fibrosis causes pulmonary symptoms to appear early in life. These include airway inflammation and impaired mucociliary clearance leading to consequent chronic infection of the airways with polymorphonuclear cells present in the bronchoalveolar lavage fluid obtained from even healthy-looking infants with CF. There is progressive decline of lung function, specifically forced expiratory volume in 1 second (FEV₁), with episodes of acute worsening of respiratory symptoms, often referred to as “pulmonary exacerbations”. Waters and co-workers¹ have recently shown for the first time that pulmonary exacerbations are responsible not only for half of FEV₁ decline, but also that the time



between consecutive exacerbations plays an important part in this long-term lung function decline¹ (Waters 2012). Due to their persistency and chronicity, these episodes progress to bronchiectasis, gas trapping, hypoxemia and hypercapnia becoming the hallmark of cystic fibrosis lung disease. Pulmonary complications of CF are responsible for 85% of the mortality of these patients. Clinical features of a pulmonary exacerbation may include increase cough, wheezing, increased sputum production, shortness of breath,

chest pain, loss of appetite, loss of weight and lung function decline.

After a rapid colonization by Haemophilus influenza or Staphylococcus aureus, at the beginning of the disease, within a short time Pseudomonas aeruginosa becomes the predominant organism found in the airways of these patients. Another organism that can cause colonization without invasive infection is Aspergillus fumigatus. An intensive allergic response to this fungus, known as allergic bronchopulmonary aspergillosis (ABPA) is seen in 1-15% of patients with CF with a frequency that varies geographically. Persistent infections enhance the genetic defect that induces dehydration of the airway surface liquid and impairs mucociliary clearance; as a result individuals with CF have difficulty clearing pathogens from the lung and experience chronic pulmonary infections and inflammation.

2. Treatment of Cystic Fibrosis

Newly introduced therapies and aggressive management of the lung disease have resulted in great improvement in length and quality of life, with the result that the median expected

survival age has reached 36 years. The recommendation of an aggressive approach is supported by the evidence coming from two epidemiological studies showing that cystic fibrosis centres with high median pulmonary function test results saw patients more frequently, obtained more frequent respiratory-tract cultures and used more oral and intravenous antibiotics than did centres with lower median lung function results^{2,3}. The US Cystic Fibrosis Foundation gave the highest recommendation for chronic pulmonary CF therapy for inhaled dornase alfa (recombinant human DeoxyriboNuclease: given daily) and for inhaled tobramycin (300 mg twice daily given in 28-day on-off cycles for use in patients with moderate to severe disease with *P. aeruginosa* in their airways)⁴. Even though evidence supporting the benefit of these two treatments in patients with CF with milder lung disease are less robust the US Cystic Fibrosis Foundation guidelines however recommend their use. Other treatments supported by this guideline are inhaled hypertonic saline, chronic azithromycin, ibuprofen and inhaled β 2-agonists in specific patient populations.

Inhaled dornase alfa (recombinant human DeoxyriboNuclease)

Inhaled dornase alfa was developed to degrade the large amount of free DNA that accumulate within CF mucus, thereby improving the viscoelastic properties of airway secretions and promoting airway clearance. Its chronic use is strongly recommended on the basis of good quality evidence derived from both short and long term studies with large numbers of patients recruited. Long term studies uniformly demonstrated improvement in lung function: increased 5.8 % compared with placebo after 24 weeks of therapy in one study⁵ and 7.3% in patients with severe CF lung disease treated for 12 weeks in another⁶. In all the studies dornase alfa was well tolerated with very few adverse events.

Inhaled antibiotics

Aerosolized antibiotics have been advocated both for eradication of initial infection and for suppression of chronic infections of the most common bacteria isolated in sputum of CF patients, particularly *Pseudomonas aeruginosa*. Perhaps the most commonly used inhaled antibiotic is tobramycin. Outcomes measured in tobramycin studies were both lung function FEV1 assessment and prevention of pulmonary exacerbations. In three studies with 619 patients in total in comparison with placebo and standard treatment, significant improvements in FEV1 ranging from 7.8 to 12% were shown^{7,8,9}. Ramsey and coworkers found that inhaled tobramycin produced a 26% reduction in hospitalization and a 36% reduction in the use of intravenous antipseudomonal antibiotics compared to placebo. In another study the total number of days spent in hospital for exacerbation treatment was less in patients treated with inhaled tobramycin in comparison with placebo⁸. On the basis of this compelling evidence, the recommendation of the benefit of tobramycin was extended also to CF patients with mild disease.

Other inhaled antibiotics are used to treat patients with cystic fibrosis, including aztreonam, which was approved by the FDA in 2010 and colistin. Both are used to treat *Pseudomonas aeruginosa* infection.

Hypertonic saline

Inhaled hypertonic saline, as a hyperosmolar agent, has been proposed as a therapy to increase hydration (drawing water into the airways) of the surface liquid of the airways (periciliary layer) in patients with CF, thereby improving mucociliary clearance. Elkins and colleagues, for example, in their large multicenter study found that patients with CF who received 4 ml of 7% hypertonic saline twice daily via nebulisation for 48 weeks had a larger increase in FEV₁ and fewer pulmonary exacerbation than patients who receive normal (0.9%) saline¹⁰.

Chronic azithromycin

Macrolide antibiotics have been used with good results in diffuse panbronchiolitis, a disease that shares similarities with pulmonary CF. The mechanism of action may be related to either the antimicrobial or anti-inflammatory properties of these agents or perhaps to both. In the largest of the four studies conducted with the chronic use of macrolides in CF, FEV₁ was improved and pulmonary exacerbations reduced after treatment with thrice weekly azithromycin compared to placebo¹¹.

Bronchodilators

Both short acting and long acting inhaled β 2-agonists have been tested in CF trials. The short acting inhaled β 2-agonist salbutamol has been administered at daily doses ranging from 80 to 600 μ g by metered dose inhaler or from 0.5 to 5mg by nebulizer while long acting inhaled β 2-agonist, salmeterol, has been administered at daily doses ranging 84 to 336 μ g by metered dose inhaler. Inhaled β 2-agonists consistently demonstrated an improvement in lung function in short term studies ranging from 2 days to 4 weeks; this benefit was not however confirmed in long term studies. When inhaled long acting β 2-agonists were compared with short acting β 2-agonists a greater improvement on FEV₁ was found. These positive results were not repeated when a short acting anticholinergic drug, ipratropium bromide, was used.

Anti-inflammatory agents

As inflammation is one of the pathophysiological features of the airways in CF, anti-inflammatory therapies are often used in the treatment of these patients. It is thought that excessive and persistent inflammation that characterizes the airways of patients with CF is a major cause of airway destruction over time leading to bronchiectasis and severe obstructive airway disease.

- ✓ **Non steroidal anti-inflammatory drugs (NSAID).** High dose oral ibuprofen has been studied in two large long-term placebo controlled trials. Konstans and colleagues in a single centre study showed a decrease in the rate of loss of lung function over 4 years in comparison with placebo, with the largest benefit seen in younger patients aged 5-13 years¹². In one Canadian multi centre study, Lands and co-workers showed no significant effect of ibuprofen treatment on FEV₁ compared to placebo, although the ibuprofen-treated group spent fewer days in the hospital than patients in the placebo group¹³.
- ✓ **Inhaled Corticosteroid (ICS).** Some ICSs have been evaluated in the treatment of CF in studies with lung function decline and pulmonary exacerbation frequency as endpoints. Results of studies with beclomethasone, fluticasone and budesonide have been negative. Therefore, ICS therapy is not recommended for the treatment of CF.
- ✓ **Oral corticosteroids.** No convincing evidence was found in studies conducted with oral corticosteroids given in an alternate day dosing schedule. Although some benefits on lung function have been reported, such therapy has been associated with adverse events related to steroid treatment which result in a net negative effect for the patients.

3. Treatment of Pulmonary Exacerbations

Treatment for pulmonary exacerbations of cystic fibrosis generally includes inhaled, intravenous or oral antibiotics, increased use of airway clearance techniques and improved nutrition¹⁴.

Combination antibiotic treatment with agents that have different modes of action is preferred to single agent treatment to avoid the emergence of resistant strains, with treatment lasting about 14 days. Since most patients with exacerbations will have *P. aeruginosa* in their airways, the usual in-hospital treatment is a combination of a β lactam, which interferes with cell wall biosynthesis, and an aminoglycoside, which binds bacterial ribosome subunits and inhibits protein production, however addition or substitution of other antibiotics specific for *S. aureus*, *H. influenza* or methicillin-resistant *S. aureus* (MRSA) might be necessary. For milder exacerbations a combination of home-based treatment of an oral and inhaled antibiotic allows the patient to continue his/her daily life unimpeded.

There are many techniques that are used with CF patients to augment clearance of tenacious airway secretions. These methods include introduction of, or prescription of a more intensive regime of, treatments such as percussion and postural drainage, positive expiratory pressure (PEP) devices, high pressure PEP devices, active cycle of breathing techniques, airway-oscillating devices, high frequency chest wall oscillation devices and autogenic drainage (i.e. chest physiotherapy in which the patient produces a series of

respiratory huffs and coughs designed to move mucus from distal to proximal airway so it can be coughed out).

The benefits of maintaining good nutrition in regard to long-term survival and lung health cannot be overstated, especially because of the strong correlation that exists between nutritional status and pulmonary function. Patients' height and weight should be measured and their body-mass index (BMI) calculated at every cystic fibrosis clinic visit; those showing a decrease in BMI or stunting should receive nutritional counseling.

4. Pulmonary Complications

As airways disease worsens there is an increased likelihood of respiratory complications, such as hemoptysis and pneumothorax¹⁵. Hemoptysis is quite common in CF patients; a retrospective review reported that 9.1% of patients had hemoptysis over a 5-year period. The average annual incidence of pneumothorax is 0.64%. Both of these complications occur more commonly in older patients with advanced disease.

Hemoptysis should be treated properly with antibiotics, always admitted to the hospital when it is massive, undergo bronchial artery embolization (BAE) when hemoptysis reaches the classification of 'massive' (coughing up ≥ 600 mL of blood in a 24 hour period) and if the patient is clinical unstable.

Patients with CF with a large pneumothorax should be admitted to hospital and should have a chest tube placed. If pneumothorax is recurrent, such patients should undergo surgical pleurodesis to prevent recurrence. After a pneumothorax episode patients with CF should avoid flying, lifting weights and spirometry for two weeks after the pneumothorax has resolved.

5. Lung Transplantation

Lung transplantation is the final therapeutic option for CF patients with end-stage lung disease. Lung transplantation has the potential to extend and substantially improve quality of life in properly selected patients. For adults referral for transplantation generally occurs when a patient's FEV₁ plateaus at less than 30% of that predicted. However age, sex, lung infection and colonization, and a rate of decline in FEV₁ all affect the decision. Use of nocturnal non-invasive ventilation can improve chest symptoms, sleep-associated hypoventilation and quality of life in patients with awake hypercapnia who are awaiting transplantation.

6. Conclusions

Today, almost 45 percent of the cystic fibrosis population is aged 18 years or older even though they still have a shorter-than-normal life expectancy. The good news is that as treatments for CF improve, the life expectancy for people with the disease is rising. Fifty

years ago, children with CF often died before attending primary school. Today many people with the disease live into their 30s, 40s and beyond.

Although refinements of conventional, symptomatic therapy will continue, and probably be enhanced by the clinical engineering so popular nowadays, great leaps in survival will require entirely new approaches to therapy. Today there are more than two dozen therapies at various stages of clinical trials, a dozen of them directed at the basic defect. Probably the latter together with the identification and treatment of patients at birth, before lung damage occurs, will allow to further increase life expectancy, at least for patients whose lungs are clear enough to benefit of them.

7. About the Author

Renato Testi graduated from the University of Padua with a degree in Chemistry, before gaining his MD from the University of Verona. After a couple of years at Padua University as an assistant in the Organic Chemistry Department, Renato joined Laboratory Glaxo S.p.A. (Italy) as Head of Chemistry from 1974 to 1979. In 1979 he moved to the Medical Department as a Medical Advisor, subsequently becoming Medical Respiratory Leader in the same company Glaxo Smith Kline SpA (Italy) from 1979 to December 2004. In this role Renato supported clinical development and marketing activities of several drugs in respiratory medicine.



In 2006, Renato became a Clinical Research Physician at Centro Ricerche Cliniche, Policlinico BG Roma, Verona focusing on performing medical activities and screening visits for volunteers involved in clinical trials in Phase I to III. Renato joined CROMSOURCE in 2010 as a Medical Monitor in the Clinical Research division. Here Renato has managed clinical trial activities, medical oversight and monitoring procedures for many international clinical trials in both asthma and COPD.

Renato continues practising as a physician specialised in respiratory medicine, currently at Unit-Policlinico BG Roma, Verona University. Renato can be contacted at renato.testi@cromsource.com

8. References

- 1) Waters V., Stanojevic S., Atenafu EG., Effect of pulmonary exacerbation on long-term lung function decline in cystic fibrosis. *Eur. Respir. J.* 2012; 40: 61-66.
- 2) Padman R., McColley SA., Miller DP., et al. Infant care pattern at epidemiologic study of cystic fibrosis sites that achieve superior childhood lung function. *Pediatrics* 2007; 119: E531-37

- 3) Johnson C., Butler SM., Konstant MV., et al. Factor influencing outcomes in cystic fibrosis: a center based analysis. *Chest* 2003, 123. 20-27
- 4) Flume PA., O'Sullivan BP., Robinson KA., et al. Cystic Fibrosis Pulmonary Guidelines. Chronic medications for maintenance of lung health. *Am. J. Respir. Crit. Care Med.* 2007; 176: 957-969.
- 5) Fuchs HJ., Borowitz DS., Christiansen DH., et al. Pulmozyme study group. Effect of aerosolized recombinant human DNase on exacerbation of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N. Engl. J. Med.* 1994; 331: 637-642.
- 6) McCoy K., Hamilton S., Johnson C., et al. Effect of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest* 1996; 110. 889-895.
- 7) Ramsey BW., Pepe MS., Quan JM., et al. Cystic Fibrosis Inhaled Tobramycin Study Group. Intermittent administration on inhaled tobramycin in patients with cystic fibrosis. *N. Engl. J. Med.* 1999; 340: 23-30.
- 8) MacLusky IB., Gold R., Corey M., et al. Long-term effect of inhaled tobramycin in patient with cystic fibrosis colonized with *Pseudomonas aeruginosa*. *Pediatric. Pulmonol.* 1989; 7: 42-48.
- 9) Ramsey BW., Dorkin HL., Eisenberg JD., et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N. Engl. J. Med.* 1993; 328: 1740-1746.
- 10) Elkins MR., Robinson M., Rose BR., et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N. Engl. J. Med.* 2006; 354: 229-240.
- 11) Saiman L., Marshall BC., Mayer-Hamblett N. et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA* 2003; 290: 1749-56.
- 12) Konstan MW., Byard PJ., Hoppel CI., et al. Effect of high-dose ibuprofen in patient with cystic fibrosis. *N. Engl. J. Med.* 1995; 332: 848-54.
- 13) Lands LC., Milner R., Cantin AM., et al. High-dose ibuprofen in cystic fibrosis: Canadian safety and effectiveness trial. *J. Pediatr.* 2007; 151: 249 -54.
- 14) Flume PA., Mogayzel PJ., Robinson K., et al. Cystic fibrosis pulmonary exacerbation guidelines. Treatment of pulmonary exacerbations. *Am. J. Respir. Crit. Care Med.* 2009; 180: 802-808.
- 15) Flume PA., Mogayzel PJ., Robinson K., et al. Cystic fibrosis pulmonary guidelines. Pulmonary complications: Hemoptysis and Pneumothorax. *Am J Respir Crit Care* 2010; 182: 298-306.

9. About CROMSOURCE

CROMSOURCE is the leading independent provider of clinical life science research services to the Pharmaceutical, Biotechnology and Medical Device industries.

Operating through offices across all regions of Europe and North America CROMSOURCE delivers a comprehensive breadth of services. We seamlessly move biopharmaceutical products from first in human conducted in our exceptional early phase unit, through all subsequent phases of pre- and

post-approval research internationally. Our Medical Device experts oversee projects through regulatory strategy and submission, to pilot and pivotal clinical investigations in Europe and North America. Our Staffing Solutions team ensures that high quality professionals are available to support your work whenever you need more resources.



Passionate about your projects.
High quality, on time, on budget.
Guaranteed.

**It's a simple concept, really.
Quality data. On time.
On Budget. Guaranteed.**

At CROMSOURCE we believe experts should keep their word. After 18 years of success we provide the industry's only End-to-End Guarantee™. Starting at the RFP stage with our uniquely detailed Feasibility Plus™ process we guarantee:

- 1. Your study will start on time**
- 2. We will enroll 100% of the contracted patients**
- 3. We will finish on time with a set date for database lock**
- 4. The price you contracted is the price you pay.**
There will be no CRO-initiated changes-in-scope.

We know that budgets must be competitive, and you can rest assured that our End-to-End Guarantee™ does not come with a premium price. As an ISO-certified organization, you can also rest easy about quality.

**Don't you owe it to your project to learn more?
Contact us to request more information.**

 **END-TO-END GUARANTEE™**
TIME, COST & QUALITY GUARANTEED

1 **ONE TRIAL ONE PRICE™**
GUARANTEED FIXED PRICE BUDGET

 **FEASIBILITY PLUS™**
GUARANTEED ENROLMENT & TIMELINES

CROM
SOURCE
advise | agree | deliver

North American Headquarters:

One Alewife Center, Suite 120
Cambridge, MA 02140 - USA
Phone +1 617 871 1128

European Headquarters:

Via Giorgio De Sandre, 3
37135 Verona - Italy
Phone +39 045 8222811

e-mail us at:

cromsource@cromsource.com

www.cromsource.com