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AEROSOLIZED AGENTS FOR AIRWAY CLEARANCE IN CYSTIC FIBROSIS

Running title: Airway clearance agents in cystic fibrosis

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Running head

Aerosolized airway clearing agents in CF

Abstract

The outlook for people with cystic fibrosis (CF) has improved considerably as a result of conventional therapies including aerosolized agents for airway clearance. These will continue to play a significant role in maintaining well-being and improving survival, even as newer agents emerge that correct the underlying CF defect. In this review, we explore the evidence supporting the use of dornase alfa, hypertonic saline and mannitol in improving mucus clearance in patients with CF from different age groups with differing disease severity. We also discuss the clinical use of these agents in the context of available international guidelines as well as practical considerations in the clinic,

highlighting the importance of a multi-disciplinary approach and shared decision making. Unanswered questions regarding the optimal use of these agents are highlighted.

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Introduction

The pathophysiology of cystic fibrosis (CF) originates from mutation of the CF transmembrane conductance regulator (*CFTR*) gene, which leads to an absence or malfunction of CFTR protein. The abnormal CFTR protein disrupts ion transport across cell membranes, resulting in dehydration of the airway surface liquid (ASL) and altered mucus properties and clearance (**Figure**)[1-3]. The abnormal ASL and mucus impairs mucociliary clearance, allowing mucus accumulation and airway obstruction[1]. This results in an environment for characteristic bacterial infections, inflammation and airways damage. More than 2,000 mutations have been identified of the *CFTR* gene, categorized into seven classes based on their molecular defect[4].

Mucus accumulation in the lower airways is an important element of CF lung disease. A major component of this abnormal mucus is polymerized DNA and filamentous actin (F-actin) derived from degraded neutrophils (**Figure**)[5]. The mucus in CF is characterized by increased sputum adhesion and 'stickiness', caused by factors such as reduced pH[3] and an abnormal phospholipid balance that alters the surface properties of the secretions[5].

Conventional management of CF, including excellent nutrition and active treatment of airway infection, has been demonstrated to extend life expectancy of patients with CF beyond 40 years. Symptomatic therapies for CF lung disease include a variety of airway clearance techniques, aerosolized agents for airway clearance (mucolytics and airway hydrators), antibiotics, anti-inflammatory drugs, pancreatic replacement enzymes and vitamin supplementation[6]. A better understanding of the molecular CFTR defect has led to the development of therapies, such as the CFTR modulators ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor combinations, that correct the defect and

have proven efficacy in improving respiratory function in adolescent and adult patients with CF[6]. However, conventional therapies, including aerosolized agents for airway clearance, continue to have a pivotal role in maintaining well-being and improving survival.

This review summarizes the presentations and discussions at an independent continuing medical education (CME) webinar "Aerosolized agents for airway clearance in cystic fibrosis: When, How and Why?", and provides updated information on the airway clearance agents, reflecting different approaches across the globe. The 1.5-hour CME program included an overview of the role of aerosolized airway clearance agents and adherence issues related to aerosolized CF therapies. Additional PubMed search for randomized clinical trials and systematic reviews (published in English up to the September 2018) was conducted to support the discussion on efficacy and safety of airway clearance agents in this manuscript. Search keywords included cystic fibrosis, recombinant human DNase, dornase alfa/alpha, hypertonic saline, and mannitol; and excluded epidemiology, pre-clinical, cost-effectiveness, non-CF studies, and studies assessing various delivery methods and combination of antibiotics/airway clearance agents.

Aerosolized airway clearance agents

The aim of airway clearance agents in CF is to prevent the accumulation of mucus and facilitate clearance from the airways; this is believed to reduce the potential for bacterial infection and inflammation.

Dornase alfa (recombinant human DNAse)

Mucus in CF airways has increased viscoelasticity, due in part to the accumulation of DNA and F-actin[5]. Dornase alfa (recombinant human DNAse) has been shown to degrade DNA and decrease mucus viscosity *in vitro* and *in vivo*, confirming a beneficial effect in improving pulmonary function via a reduction in mucus viscoelasticity[7-9].

Dornase alfa was the first approved DNAse therapy for the treatment of CF lung disease and is available as a 2.5 mg dose for inhalation once daily[10]. The clinical efficacy of

dornase alfa in patients with CF has been demonstrated in several clinical trials in patients with mild-to-severe lung disease.

In adult patients with mild-to-moderate CF, administration of 2.5 mg aerosolized dornase alfa once or twice daily resulted in an improvement in lung function and a modest reduction in the risk of exacerbations of respiratory symptoms[11]. Continued administration for up to 6 months led to a mean improvement in FEV_1 of 5.8% following once-daily treatment and 5.6% for twice-daily treatment. Dornase alfa was also associated with a reduced incidence of pulmonary exacerbations, with no difference between once- and twice-daily administration[11]. In patients with *severe lung disease,* improvement in lung function was only was seen after 3 months of dornase alfa therapy, possibly suggesting a slower response[12,13].

Longer term studies suggest a continued benefit from dornase alfa on the rate of decline of FEV_1[14]. A Cochrane systematic review of dornase alfa for CF confirmed its role in improving lung function and decreasing exacerbations when compared with placebo – improvements in FEV_1 were observed within one month of initiating dornase alfa[15]. Post-marketing surveillance in Europe confirmed the findings from clinical trials in routine clinical practice – dornase alfa improves lung function and reduces the incidence of exacerbations[16].

In addition to reducing pulmonary exacerbations, dornase alfa has been shown to influence the progression of neutrophilic airway inflammation that is seen in untreated patients with CF. The study by Paul *et al*. found that dornase alfa treatment did not alter the percentage of neutrophils in the bronchoalveolar lavage fluid neutrophils, in contrast to the increase seen in untreated patients[17]. The anti-inflammatory effect of dornase alfa may be an indirect consequence of the lower rate of exacerbations or the improved mucus clearance[17,18].

In a 2-year study of young patients with CF (6–10 years) and mild lung disease, dornase alfa maintained lung function and reduced the risk of exacerbations[19]. In a short (4 week) cross-over study, a Canadian group demonstrated a small but significant reduction in lung clearance index with dornase alfa compared to placebo in children with CF between 6 to

18 years of age[20], further supporting a possible role for dornase alfa in a young population with milder airway disease.

The Cochrane review concluded that there is paucity of data on the efficacy of dornase alfa in improving lung function in children under the age of 6 years[15]. While the data from the Epidemiologic Registry of CF suggests that dornase alfa is well-tolerated in children with CF under 5 years of age[21], more studies are needed to confirm the benefit of dornase alfa in the pre-school age children.

In clinical trials, dornase alfa was well-tolerated and post-marketing surveillance has been reassuring. Voice alteration and rash were the most commonly reported adverse events[15,16].

With respect to timing and frequency of dornase alfa administration, current evidence based on a small number of participants suggests no difference when administered before or after airway clearance techniques[22]. Limited evidence also suggests no difference in improvement in lung function or symptoms when dornase alfa was administered in the morning or evening; daily and alternate-day; or once and twice a day[11,22,23]. In the absence of high-quality evidence, the decision on timing and frequency of dornase alfa use may depend on practical reasons or individual preference of the patient. Alternate-day use could potentially reduce treatment burden and cost in patients with CF[23]. While there were no safety concerns over inhalation of dornase alfa prior to bedtime in young patients, this practice in older and more severe patient populations could potentially lead to large amount of mucus being released but not properly cleared during sleep[24]. As such, it is important to create an individualized treatment plan that is convenient, acceptable and maintainable for each patient.

Mucus hydrators: hypertonic saline and mannitol

Administration of agents, such as hypertonic saline and dry powder mannitol, creates an osmotic gradient which draws water into the airway and rehydrates the ASL, increasing mucociliary clearance[25]. Osmotic agents have a different and possibly complementary mechanism of action to dornase alfa[26].

Hypertonic saline

Hypertonic saline (3–7% sodium chloride [NaCl] solution) has a higher osmotic pressure than isotonic saline (0.9% NaCl) solution and is administered via a nebulizer[25]. In a randomized controlled trial comparing twice-daily administration of either hypertonic or isotonic saline over 48 weeks, there was no significant improvement in the primary outcome (rate of decline of FEV_1), but some improvement in other secondary outcomes that may be important to people with CF, such as exacerbation rate. Participants who were allocated hypertonic saline had reduced frequency of pulmonary exacerbation and improved quality of life[27]. Furthermore, the effect of hypertonic saline was similar in those who used and did not use dornase alfa[27]. A Cochrane systematic review confirmed that hypertonic saline had limited effect on lung function, but improved quality of life and reduced pulmonary exacerbations[28].

It has been suggested that hypertonic saline can be administered before or during airway clearance techniques to potentially augment these strategies. Recent data from a small pilot study reported that there was no difference in lung clearance index when hypertonic saline was administered before or during airway clearance[30].

The Infant Study of Inhaled Saline (ISIS) study examined hypertonic saline versus isotonic saline in 321 pre-school children with CF (between the ages of 4–60 months) and did not identify any significant difference in respiratory exacerbations, although both aerosols were well tolerated[31]. Hypertonic saline also resulted in a significant change in $FEV_{0.5}$ in these children, suggesting a potential improvement in the airflow. However, further study with sensitive endpoints is warranted[31].

Hypertonic saline has a good safety profile and acceptable tolerability in young and adult patients with CF. Some patients may experience oropharyngeal irritation, wheeze and bronchospasm, especially with higher concentrations and faster delivery[32]. Pre-treatment with a bronchodilator is recommended.

Mannitol

Dry powder mannitol, a naturally occurring monosaccharide, has a similar osmotic effect to hypertonic saline and potentially hydrates the ASL when inhaled. Unlike dornase alfa and hypertonic saline, mannitol does not require refrigeration, nebulization, or routine equipment sterilization, thereby providing a more convenient treatment option[33]. Similar to hypertonic saline, inhaled mannitol can stimulate coughing and induce bronchospasm[34].

Data from two randomized controlled trials comparing twice-daily inhaled mannitol to a placebo (very low dose mannitol for taste masking) demonstrated a small but significant improvement in FEV_1 and a reduction in pulmonary exacerbation with no significant increase in the reporting of adverse events[35,36]. Sub-group analysis suggested that the benefit in respiratory function was limited to adults and not apparent in children or young adults[37].

In a subsequent study of children with CF aged 6–17 years, inhaled mannitol was well tolerated and associated with improvement in lung function and a decreased incidence of pulmonary exacerbations, irrespective of disease severity[38].

A Cochrane systematic review concluded that there was moderate quality evidence that inhaled mannitol improved lung function over a 6-month treatment period, and limited evidence of improved quality of life in patients with CF[39].

Dry powder mannitol is delivered via a breath-actuated device and therefore some patient technique is required[14]. An exploratory study was reassuring that the generation of optimal flow for mannitol inhalation was not an issue in patients with CF[40].

Direct comparisons between aerosolized airway clearance agents

There have been no direct comparative effectiveness studies evaluating the three muco-active agents described above. There has been some sub-group analysis of data within studies, but Cochrane systematic reviews have concluded that there is no high-quality evidence to recommend one agent above another[15,39]. The choice of muco-active agent is

therefore one that requires a degree of clinical judgement. It is important that these decisions are made in partnership with patients with CF and their families and that all options are considered. Although all members of the multi-disciplinary team have a role in determining the best treatment regimen for an individual patient, the physiotherapist has a particularly important contribution to make, both in assessing new therapies and evaluating responses to specific interventions. The physiotherapist should assess a thorough history and direct observation of delivery as to which intervention the person with CF feels is most effective. There are several factors to assess in this process and physiotherapists are ideally placed to work in partnership and decide on the best option for an individual.

Clinical use of airway clearance agents

Guideline recommendations

In general, available guidelines for the management of CF recommend consideration of the use of dornase alfa and hypertonic saline as a routine component of airway clearance therapy for older patients with CF. In children below 5 years of age, dornase alfa and hypertonic saline should be considered based on an individual basis.

The European Cystic Fibrosis Society (ECFS) best practice guidelines consider dornase alfa as the only mucolytic agent with proven efficacy in CF and recommend long-term maintenance therapy with dornase alfa to maintain treatment effect[26]. The guidelines indicate potential use of hypertonic saline and mannitol in patients with CF – hypertonic saline is used in many patients with moderate-to-severe lung disease and is recommended by the CF Foundation guidelines, while the recently introduced mannitol has been shown to improve lung function and its powder formulation can potentially reduce treatment time[26]. Since both agents can result in bronchospasm, the guidelines recommend pre-treatment with a bronchodilator and tolerability testing prior to their long-term use[26].

The UK National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis and management of CF recommend dornase alfa as the first choice of muco-active agent[41]. If clinical response is inadequate, hypertonic saline, alone or in combination with dornase alfa, should be considered. Dry powder mannitol for inhalation

is recommended as an option in adults with declining lung function, who are intolerant of or have an inadequate response to dornase alfa, and for whom other osmotic agents are not considered appropriate[41].

The guidelines published by the CF Foundation in the US recommend the long-term use of dornase alfa to preserve lung function and reduce exacerbations in patients with moderate to severe lung disease. Dornase alfa is also recommended for patients with asymptomatic or mild lung disease[42]. The chronic use of hypertonic saline was also recommended for individuals with CF, 6 years of age and older; whereas no recommendation was made for mannitol[42]. Based on the moderate quality evidence for children under the age of 5 years old, the CF Foundation guidelines recommend that dornase alfa use in these young patients be considered based on individual circumstances[43,44]. Similarly, inhaled hypertonic saline in patients aged 2–5 years should be selectively used based on individual assessment[44].

In Australia, hypertonic saline is administered widely and without restriction with efficacy determined by patients, families and the care team. The subsidized use of dornase alfa and mannitol is guided by criteria from the Pharmaceutical Benefits Scheme. Subsidized use of dornase alfa is limited to 3 months at a dose of 2.5 mg daily. For continued use, patients need to demonstrate clinical benefit and no deterioration of FEV_1. Initiation of subsidized dornase alfa therapy in patients under 5 years of age is limited to those who have severe clinical conditions, including frequent exacerbations, significant bronchiectasis, CF bronchiolitis non-responsive to conventional medicines, and severe physiological respiratory deficit[45]. Subsidized mannitol is generally used in patients with CF 6 years of age or older who are intolerant or inadequately responsive to dornase alfa. Initial mannitol therapy is limited to 3 months at a dose of 400 mg twice-daily. Continued use of mannitol depends on achieving criteria similar to those of dornase alfa[46].

Optimizing treatment outcomes for patients with CF

Dornase alfa is approved in Europe, the US and Australia. Hypertonic saline is commonly used in Europe, US and Australia. Mannitol is approved for use in Europe and Australia but is not yet approved by the US FDA.

Due to the insufficient high-quality evidence to determine the superiority of one agent over the other[15,39], guidelines generally do not provide any recommendations on which agent should be initiated first. Evidence comparing inhaled dornase alfa and hypertonic saline is low quality; however, supported by clinical expertise and experience, the NICE guideline committee considered dornase alfa as more effective and tolerable compared with hypertonic saline and that there was insufficient evidence to change the currently accepted practice[41]. As such, the guideline recommends dornase alfa as the first treatment choice[41].

As these agents have different mechanisms of action, there may be benefit from using more than one[24]. The effect of hypertonic saline was independent of dornase alfa[27], while pooled data suggested that mannitol may provide additional benefit in improving lung function in patients who were already treated with dornase alfa[37].

Whilst there is a clear indication for the use of muco-active agents in older patients with established CF airways disease, the evidence base is less robust in patients with minimal or no detectable airways disease. In these patients, it is important to have open and clear discussions with the patient and their family and involve them in joint decision making. Not engaging with the patient and family will have a negative influence on adherence to these long-term therapies. There should be clear consideration to the factors impacting on adherence, including daily routine and resources in the family. Visual aids, such as chest imaging (X-rays and high-resolution computerized tomograms [HRCT]) and bronchoscopy recordings, may act as modalities that can be used to explain the rationale for long-term aerosolized therapy and promote adherence.

Adherence

Treatment adherence is important for improving patient outcomes but adherence rates to aerosolized agents for airway clearance are generally low. The reported adherence to dornase alfa was 59%; however, this was measured based on prescription fills and not observed medication use[47]. In another study, 82% of patients with CF claimed to use dornase alfa more than 20 days/month, but only 24% of patients were recorded to collect sufficient prescriptions[48], highlighting the difficulty in accurately measuring treatment

adherence. The adherence to hypertonic saline and dornase alfa in children ranged between 55–83%, with lower adherence rates in older age group (13–21 years old)[49]. To enhance adherence, it is important for the CF team to understand the factors influencing adherence patterns, such as patient's perception and understanding of disease, patient's age, treatment complexity, and family support[50]. The CF team should utilize all available tools to support families and engage in shared decision making to optimize success on an individual basis[50,51].

Aerosolized agents for airway clearance in CF

- Aerosolized dornase alfa is an established component of CF care, with good quality evidence of a significant effect on respiratory function in people with CF who have moderate or severe airways disease. It is well tolerated but requires commitment from the patient for successful long-term adherence.
- Hypertonic saline has been shown to be an effective and safe therapy for older children and adults with CF and is a low-cost intervention. Hypertonic saline is used in patients with moderate-to-severe lung disease and is recommended by guidelines.
- Mannitol is an alternative osmotic agent, with evidence suggesting benefit in older children and adults with CF. Long-term impact of mannitol remains to be established, but its dry powder formulation provides a more convenient treatment option.

Questions to be answered

There are several questions concerning the currently available muco-active agents:

- What is the optimal dose and frequency of dornase alfa to reduce treatment burden in patients with CF and optimize adherence?
- Does twice-daily use of dornase alfa in patients with pulmonary exacerbations or severe lung disease provide additional benefit?
- What is the role of dornase alfa, hypertonic saline and mannitol in asymptomatic patients with no evidence of airways disease?
- Does the early use of muco-active agents (dornase alfa, hypertonic saline and mannitol) simply arrest the progress of CF airways disease or are these agents

disease-modifying (i.e., would early use of any of these agents prevent the onset of bronchiectasis)?

In summary, dornase alfa, hypertonic saline and mannitol are inhaled agents that have each been shown to demonstrate pulmonary benefits in CF by improving mucus clearance, which is a primary defect in CF. Their relative effectiveness (alone or in combination) has not been clearly established, but they all represent viable treatment options to manage airway disease in CF. Successful long-term use of these agents depends on clear partnership – working with patients with CF and their families to engage in shared decision making, for improved adherence and better outcomes.

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Figure

Figure. Airway surface liquid (ASL) dehydration in cystic fibrosis. The malfunctioning of CFTR protein, accompanied by fluid absorption via the epithelial sodium channel (ENaC), disrupts ion transport and water efflux across cell membranes, resulting in dehydration of the ASL and abnormal mucus. Mucociliary clearance impairment leads to mucus accumulation and airway obstruction, and inflammation due to bacterial invasion. Airway clearance agents, such as rhDNase degrades the polymerized DNA from dead and dying neutrophils in CF mucus (inset); while mucus hydrators, such as hypertonic saline and mannitol, draw water into the airway by creating an osmotic gradient[1-3,5].