Inhaled medication other than antibiotics

Chronic use of dornase alfa (pulmozyme) in patients > 6 years old

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Background

In cystic fibrosis (CF) lung disease, there is significant neutrophil influx into the airways. As these neutrophils undergo apoptosis, they release large quantities of DNA, which increases sputum viscosity and impairs ciliary transport. The resulting viscous secretions lead to mucus plugging, perpetuating cycles of infection and inflammation.

Dornase alfa (Pulmozyme®) is a highly purified solution of recombinant human deoxyribonuclease I (rhDNase). When administered by inhalation at 2.5 mg once daily, it reduces sputum viscosity, thereby facilitating mucus clearance. The mechanism of action involves cleavage of extracellular DNA in the airways, which directly relieves airway obstruction—a key rationale behind its development—resulting in significant improvements in lung function. Additionally, dornase alfa reduces the risk of pulmonary exacerbations and infections requiring intravenous antibiotics, likely through improved mucociliary clearance and broader effects on host defense mechanisms.

Observational registry-based studies have demonstrated that patients receiving dornase alfa experience modest clinical benefits, with a favorable safety and tolerability profile across all age groups. Furthermore, initiation of dornase alfa therapy results in acute improvement in forced expiratory volume in one second (FEV?), and consistent use is associated with attenuated annual decline in FEV? over a two-year period.

A recent single-center study evaluated the impact of discontinuing nebulized dornase alfa on lung clearance index (LCI) in school-age children with CF who were not receiving CFTR modulators or hydrator therapy (Voldby C, 2021). One month of dornase alfa withdrawal resulted in increased ventilation inhomogeneity and deterioration in FEV? and FEF??–?? in children with mild CF lung disease.

The evidence supporting the efficacy and mechanisms of action of dornase alfa has been comprehensively reviewed in recent publications (Southern KW, 2019) and (Terlizzi V, 2022).

Based on available evidence, dornase alfa is recommended in the Cystic Fibrosis Foundation Guidelines as a standard therapy for children aged six years and older with mild to severe lung disease (Mogayzel Jr. PJ, 2013). It is also included in the European Cystic Fibrosis Society standards of care (Burgel PR, 2024).

Despite these recommendations, dornase alfa utilization varies considerably across countries. In the United States, the Cystic Fibrosis Foundation Patient Registry reported that 92.4% of patients aged six years and older used rhDNase in 2019. In Europe, usage rates demonstrate substantial variation, ranging from 67% in the United Kingdom to 50% in Germany and 37% in Italy. In recent years, these utilization patterns have shifted following the introduction of CFTR modulators. By 2023, the proportion of patients aged six years and older using rhDNase had declined to 82.9% in the United States, 61.4% in the United Kingdom, and 36-42% in German children and adults, respectively.

A recent study utilizing national registry data compared longitudinal lung function trajectories in children with CF in the United States and United Kingdom. The analysis demonstrated that US children homozygous for the F508del mutation had superior lung function compared to their UK counterparts, a difference primarily attributed to earlier initiation of therapies including dornase alfa and hypertonic saline (Schluter DK, 2022).

Finally, in 2020 the biosimilar medicinal product Tigerase ® (dornase alpha) (Generium JSC, Russia) and the reference medicinal product Pulmozyme ® (F.Hoffmann-La Roche Ltd, Switzerland) were compared with the purpose of establishing their comparability for symptomatic treatment of patients with CF. During long-term treatment of patients with CF, no statistically significant differences were found in terms of efficacy (changes in FEV 1 and FVC; number of exacerbations of chronic pulmonary disease and the number of days before its development; change in body weight; quality of life) between medicinal products. A safety analysis demonstrated the comparability of medicinal products in terms of the incidence of adverse events (Amelina E, 2020)

Issues

1. To determine whether there is evidence of benefit in using dornase alfa in people with CF in terms of a reduction in morbidity or mortality.
2. To identify any adverse events associated with the use of dornase alfa.
3. To compare the efficacy of dornase alfa with other mucolytics (such as hypertonic saline, acetylcysteine and mesna).
4. To determine the effect of timing of dornase alfa inhalation on measures of clinical efficacy in people with cystic fibrosis (in relation to airway clearance techniques or time of the day).
5. To determine the effect of dornase alfa on sinonasal problems in CF.
6. To determine the effect of withdrawing dornase alfa in CF

What is known

Regarding issues 1 - 3

A recent CDSR is available on this topics (Yang C, 2021).

There is evidence to show that, compared with placebo, therapy with dornase alfa improves lung function in people with cystic fibrosis in trials lasting one month to two years. There was a decrease in pulmonary exacerbations in trials of six months or longer. There is not enough evidence to firmly conclude if dornase alfa is superior to other hyperosmolar agents in improving lung function.

A recent review (Southern KW, 2019) explores 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 and the unanswered questions regarding the optimal use of these agents.

The effect of dornase alfa on mortality is inconclusive, because many of the trials are short-term.

Dornase alfa is well-tolerated. Voice alteration and rash appear to be the only adverse events reported with increased frequency in randomised controlled trials.

Limiting the treatment to selected groups of patients may be a more reasonable approach in practice, given the high drug cost and varied treatment response.

An observational study, based on registry data from UK (Newsome SJ, 2019), showed that DNase improved lung function in individuals with reduced lung function (ppFEV1 < 70%), bringing a step-change in lung function, but no change in the slope of decline. On the other side, there was no evidence for a benefit in lung function in those initiating treatment with ppFEV$_1$?>?70%.

Finally, another registry-based study, using data of the European CF registry (McKone E, 2020) confirms earlier work that in European patients <18 years of age, dornase alfa treatment leads to an improved rate of decline in lung function.

A research question that also in the modulator era could be significant, in particular for people with severe lung disease and/or subjects not eligible to CFTR modulation, is:

Did people with CF and received dornase alpha and Hypertonic Saline (HS) have better preserved lung function than those treated with DA only?

Two studies evaluated this issue:

1) A registry study from US, involving patients followed between 2006 and 2014 (pre-CFTR modulators era) shows that subjects with CF $_{F508del}$ had no significant difference in lung function when nebulized HS was added to dornase for 1-5 years (Kaditis AG, 2023).

2) A registry study using UK CF Registry data from 2007 to 2018, emulated a target trial. The authors included people aged 6 years and over who were prescribed DNase without HS for 2 years. Moreover they investigated the effects of combinations of DNase and HS over 5 years of follow-up. Inverse-probability-of-treatment weighting was used to control confounding. The study concluded that for individuals with CF prescribed DNase, no evidence was found that adding HS had an effect on FEV$_1$% or prescription of intravenous antibiotics. (Granger E, 2023)

Regarding issue 4

A recent CDSR is available on this topic (Dentice R, 2021)

The current evidence is insufficient to recommend inhaling dornase alfa before or after the airway clearance techniques.

Inhalation of dornase alfa for children with well?preserved lung function before airway clearance techniques may be more beneficial for small airway function, but does not affect other outcomes.

However, the timing of dornase alfa inhalation can be largely based on pragmatic reasons or individual preference.

Regarding issue 5

Nasally inhaled dornase alfa can be effective in patients with cystic fibrosis and sinonasal disease who do not respond to conventional therapy after surgical treatment. A RCT (Mainz JG, 2014) with a novel device gave promising results for the new therapeutic concept of sinonasal inhalation with vibrating aerosols. In fact, primary nasal symptoms improved significantly with dornase alfa compared with no treatment, while small improvements with isotonic saline did not reach significance. SNOT-20 overall scores improved significantly after dornase alfa compared with isotonic saline (p=0.017).

Recently, a systematic review (Shah GB, 2018) concluded that topical intranasal dornase appears to improve sinonasal symptoms in CF patients to a greater degree than saline alone. The impact on other outcomes is less clear. Larger studies are needed to fully elucidate the true efficacy of dornase alfa in the treatment of CRS in CF patients.

Regarding issue 6

- A particular point of view is the effect of withdrawal of dornase alfa on lung funtion. One month's withdrawal of dornase alfa caused increasing ventilation inhomogeneity measured by Lung Clearance Index (LCI) and deteriorating FEV$_1$ and FEF$_{25-75}$ in school-age children with mild CF (Voldby C, 2021).
- The SIMPLIFY study aimed to assess the effects of discontinuing nebulised hypertonic saline or dornase alfa in individuals using the CFTR modulator elexacaftor plus tezacaftor plus ivacaftor (ETI). The SIMPLIFY study included two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials at 80 participating clinics across the USA in the Cystic Fibrosis Therapeutics Development Network. Individuals with cystic fibrosis aged 12-17 years with percent predicted FEV$_1$ (ppFEV$_1$) of 70% or more, or those aged 18 years or older with ppFEV$_1$ of 60% or more, if they had been taking ETI and either (or both) mucoactive therapies (?3% hypertonic saline (HS) or dornase alfa (DA)) for at least 90 days before screening were included. The main results was that in individuals with CF on ETI with relatively well preserved pulmonary function, discontinuing daily HS or DA for 6 weeks did not result in clinically meaningful differences in pulmonary function when compared with continuing treatment (Mayer-Hamblett N, 2023).

- In a SIMPLIFY substudy, gamma scintigraphy was used to determine whether discontinuation of either HS or DA was associated with deterioration in the rate of in vivo mucociliary clearance (MCC) in participants ?12 years of age. While no significant differences in MCC endpoints were associated with HS discontinuation, significant improvement in whole and peripheral lung MCC was observed after discontinuing DA. These results suggest that pwCF on ETI with mild lung disease do not experience a subclinical deterioration in MCC that could later impact health outcomes after discontinuing HS, and in fact may benefit from improved MCC after stopping DA treatment (Donaldson SH, 2024).
- On this basis, although the costs of DA and HS are smaller compared with ETI, reduction in use would lead to substantial prescription drug cost savings and reduce the treatment burden. However, individual benefits of these therapies should be considered, and decisions regarding changes in therapy remain an important discussion between people with CF and their providers (Gold LS, 2024).
- To evaluate the impact of discontinuing both hypertonic saline (HS) and dornase alfa (DA) versus continuing both therapies, a subgroup of participants in the SIMPLIFY study who sequentially participated in trials evaluating the independent clinical effects of discontinuing HS and DA was studied. Forty-three participants discontinued both therapies by the end of SIMPLIFY, and 63 remained on both. In conclusion, SIMPLIFY participants who sequentially discontinued both HS and DA experienced no meaningful changes in clinical outcomes and reported decreased treatment burden as compared with those who remained on both therapies (Mayer-Hamblett N, 2024).

Miscellanea of further clinical trials

- rhDNase was tested vs inhaled mannitol: mannitol was showed to be at least as effective as rhDNase after 3 months of treatment. The combination of mannitol and rhDNase was not useful (Minasian C, 2010). Different results were showed by a retrospective case-control study in children with CF. This study showed that in those patients who tolerated long-term (12 months) treatment with DPI, mannitol and dornase alfa made greater improvements in FEV1, FVC, FEV1/FVC, FEF25-75 z-scores than treatment with dornase alfa alone (Tural DA, 2021)
- rhDNase significantly improved Lung Clearance Index in CF patients with mild lung disease (Amin R, 2011).
- Administration of dornase alfa via an electronic nebulizer with vibrating membrane technology (eRapid nebulizer) resulted in comparable efficacy and safety, shorter nebulization times, and higher patient preference (Sawicki GS, 2015).

Unresolved questions

Further investigation is needed to examine the effects of rhDNase on longitudinal outcomes, particularly the rate of FEV? decline in CF. Future trials comparing daily dornase alfa with alternative dosing regimens (e.g., alternate-day administration) or with other mucolytic agents will likely be important.

FEV? was not affected by the timing of dornase alfa inhalation relative to airway clearance techniques or time of day. To investigate effects on small airway function, more sensitive measures such as multiple breath nitrogen washout and/or lung clearance index should be employed.

Long-term research is required to evaluate the cost-effectiveness of rhDNase over extended periods and to identify which patients would derive the greatest benefit from this expensive treatment.

A recent consideration concerns the observation that people with CF receiving highly effective CFTR modulators (ivacaftor and elexacaftor/tezacaftor/ivacaftor [ETI]) are less likely to continue concurrent therapies including inhaled antibiotics, dornase alfa, hypertonic saline, chronic oral antibiotics, and nutritional supplementation, compared to those not receiving these medications. Specifically, the differences in dornase alfa and hypertonic saline utilization between ivacaftor-treated and non-ivacaftor-treated individuals are more pronounced among those with higher baseline lung function (Granger E, 2021).

The SIMPLIFY study demonstrated that in individuals with CF receiving ETI with relatively well-preserved pulmonary function, discontinuing daily hypertonic saline or dornase alfa for six weeks did not result in clinically meaningful differences in pulmonary function compared with continuing treatment (Mayer-Hamblett N, 2023). Furthermore, people with CF receiving ETI with mild lung disease do not experience subclinical deterioration in mucociliary clearance (MCC) that could subsequently impact health outcomes after discontinuing hypertonic saline, and may actually benefit from improved MCC following discontinuation of dornase alfa treatment (Donaldson SH, 2024). Additional studies are ongoing to explore this phenomenon over extended time periods.

Until more definitive long-term evidence becomes available, treatment discontinuation decisions must be made collaboratively between CF clinicians and people with CF or their caregivers, carefully weighing the benefits of treatment rationalization against the uncertain long-term effects of discontinuation on respiratory outcomes.

In conclusion, dornase alfa remains recommended for people with CF while awaiting long-term data to support discontinuation in those receiving CFTR modulators. Dornase alfa continues to be indicated for people with CF who are not candidates for CFTR modulators, including those without eligible genetic variants, and those whose clinical condition does not improve adequately despite CFTR modulator therapy. Further long-term studies, real-world evidence collection, and biomarker research are warranted to define optimal CF treatment regimens and identify populations in whom mucoactive therapy may be safely discontinued during chronic CFTR modulator treatment.

Keywords

Airway clearance drugs -expectorants- mucolytic- mucociliary-;