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 a large influx of neutrophils into the airways. As the neutrophils die, they release large quantities of DNA causing the sputum to be thick and tenacious and decreasing ciliary transport. The thick secretions lead to mucus plugging of the airways and further cycles of infection and inflammation.

Dornase alfa (Pulmozyme®) is a highly purified solution of recombinant human deoxyribonuclease (rhDNase); when inhaled (2.5 mg/die), it reduces viscosity in the lungs, promoting improved clearance of secretions. rhDNase cleaves extracellular DNA in the airway to facilitate mucus clearance in the lung. By decreasing the size and viscosity of DNA in sputum, rhDNase has the direct effect of relieving obstruction, which was the original rationale for its development, this translating into a significant improvement in lung function. In addition to its effect on obstruction, dornase alfa also significantly reduces the risk of exacerbations or infections requiring intravenous antibiotics, probably as a result of improved mucociliary clearance and/or broader effects on host defenses against infection.

Observational studies originating from registries confirmed that patients using dornase alpha benefit slightly from the use of the drug and that the tolerability and safety profile of the drug in all age groups are good. Moreover initiating dornase alfa therapy leaded to an acute improvement in FEV1 and a consistent use of that drug was associated with an improvement in the annual rate of decline in FEV1 over a 2-years period.

A recent single center study assessed to what degree withdrawal of nebulised dornase alfa affected LCI in school-age children with CF not receiving CFTR modulators or hydrator therapy (Voldby C, 2021). One month's withdrawal of dornase alfa caused increasing ventilation inhomogeneity and deteriorating FEV_1 and $FEF_{25–75}$ in school-age children with mild CF.

The body of evidence on the efficacy of dornase alfa and its potential mechanisms was recently reviewed (Southern KW, 2019) and (Terlizzi V, 2022)

Based on the available evidence dornase alfa has been recommended in Cystic Fibrosis Foundation Guidelines (Mogayzel Jr, PJ, 2013) as a standard of treatment for children 6 years and above with mild to severe lung disease and in the standards of care of the European CF Society (Castellani C, 2018).

In spite of these recommendations, the use of dornase is very different in the different countries. In The US, the CFF Patient Registry reports in 2019 that 92.4% of patients > 6 years of age use rhDNase. In Europe, the range of patients using Pulmozyme is very wide, from 67% in the UK, to 50% in Germany and 37% in Italy.

A recent study, using national registry data, comparing longitudinal lung function in children with CF in the USA and UK showed that US children homozygous for F508del had better lung function than UK children. This difference was mainly linked to differences in the use of early treatments as dornase alfa and HS (Schluter DK, 2022)

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 or dornase alfa) 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 hypertonic saline or dornase alfa for 6 weeks did not result in clinically meaningful differences in pulmonary function when compared with continuing treatment (Mayer-Hamblett N, 2022).

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

There is a need to investigate on the effect of rhDNase on longitudinal outcomes such as rate of decline for FEV_1 in CF. It is likely that further trials comparing daily dornase alfa with other regimens (e.g. alternate day dornase alfa) or with other mucolytics will be important in the future.

FEV_1 was not affected by the timing of dornase alfa inhalation with respect to airway clearance or time of the day. To investigate the effect on small airway function, a more sensitive measure, such as nitrogen washout and/or lung clearance index, might be used.

Long term research is needed to evaluate the long term cost effectiveness of rhDNase and to identify which patients would benefit most from this expensive treatment.

A recent issue regards the fact that people with CF who are treated with highly efficient CFTR modulators (ivacaftor and elexacaftor/Tezacaftor/ivacaftor [ETI]) are less likely to continue other treatments such as inhaled antibiotics, dornase alfa, hypertonic saline, chronic oral antibiotics and supplementary feeding, compared to people who are not treated with these drugs. In particular, the differences in use of dornase alfa and hypertonic saline solution between ivacaftor-treated and non-ivacaftor-treated people, are larger for people with higher lung function (Granger E, 2021). The SIMPLIFY study has showed that in individuals with CF on ETI with relatively well preserved pulmonary function, discontinuing daily hypertonic saline or dornase alfa for 6 weeks did not result in clinically meaningful differences in pulmonary function when compared with continuing treatment (Mayer-Hamblett N, 2022). Further studies are ongoing to explore this issue on a longer period of time.

Keywords

Airway clearance drugs -expectorants- mucolytic- mucociliary-;