CF Guidelines - Nebulised Pulmozyme (Dornase Alfa)

Pulmozyme:

The thick, tenacious sputum seen in CF is due in part to the presence of DNA released from dead neutrophils. Recombinant human DNase is very effective in liquefying CF sputum in vitro and in vivo. However, clinical trials of nebulised DNase have demonstrated only relatively modest clinical improvements. Improvements have been observed in spirometric lung function, cough, dyspnoea and quality of life scores with reduced frequency of exacerbations. No survival benefit has been demonstrated.

There is significant individual variation in response, ranging from significant improvement (FEV_1 increases >20%) to the 6-30% of patients who show clinical deterioration. More difficult to identify in practise are those who fail to show an improvement in spirometry, but have an improvement in exacerbation frequency. Conversely, there are those patients who report an improvement in symptoms while having deterioration in lung function (Davies et al, 1997).

Intial studies demonstrated benefit in those with FEV_1 <80% and FVC>40%. Subsequent trials have shown benefit both in those with early disease (FEV_1 >80%) and the severely ill (FVC<40%), although longer trials may be needed in this latter group. No trial data exists for children <5yrs.

Treatment with DNase is expensive (£7200 pa in 2007) and time consuming. There is potential concern that time committed to DNAse treatment could reduce compliance with other treatments, particularly physiotherapy or nebulised antibiotic therapy. It is therefore necessary to identify individuals who have clinical benefit, from those others in whom treatment should be stopped.

Licenced indications:

"Management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted and over 5 years of age to improve pulmonary function."

Patient selection:

Early intervention (FEV_1 >80%):

- DNAse may be given as a trial in those patients with mild disease when lung function is declining, with evidence of small airways disease or a need for intravenous antibiotics. Clinicians should recognise the lack of licence in those <5 years.

Standard intervention (FVC>40%; FEV_1 <80%):

- DNAse should be given as a trial in patients with chronic cough, those with persistent growth of Pseudomonas aeruginosa in sputum, or exacerbations requiring IV antibiotics.

Advanced stage intervention (FVC<40%):

- Although outside licence, trials have shown lung function benefit in this group, although a longer 3-6 month trial period may be needed to identify those who will benefit.

Dornase Alfa Trials:

Nebulised DNase should be provided as a 1 month trial by the CF centre. The trial should be instituted by a CF consultant. The patient's GP should be informed prior to commencement of the trial. The GP should be informed that should the trial prove

beneficial they will be asked to prescribe further supplies of this expensive medication on a long term basis. They should be asked to contact the CF consultant if they are not happy with this arrangement. In all patients, compliance with other therapies must be considered prior to a trial of DNase. DNase should be presented to the patient as an adjunct to physiotherapy.

Administration:

- DNase should be nebulised using a jet nebuliser eg PARI LC or Eflow.
- DNase (Pulmozyme) should be prescribed at a dose of 2.5mg (one 2.5ml ampoule) nebulised, undiluted, once daily.
- DNase should not be mixed with any other drug in the nebuliser chamber (as this may denature the protein).
- Where other nebulised drugs are to be given, a separate nebuliser chamber should be provided for sole use with DNase.

Suggested regime for use:

- Inhaled/nebulised bronchodilator - 5 minute interval.
- Nebulised DNAse - interval of 30 minutes - 2 hours, then physiotherapy.
- Inhaled/nebulised bronchodilator, then nebulised antibiotic.

Assessment of benefit:

- If there is >8% relative improvement in either FEV_1 and FVC, then the trial shows benefit and nebulised DNase should be continued.
- If there is a fall in FEV_1 or FVC after 4 weeks, then DNase should be stopped.
- If there is a suboptimal (<8%) improvement in FEV_1 and FVC, but patient feels there is significant symptomatic benefit, then the trial may be continued for a total of 3 months to allow further time for improvement to be observed. If assessment after 2 and 3 months fails to show >8% relative improvement in either FEV_1 and FVC then DNase should be stopped.
- Where a patient has had frequent (≥4/yr) exacerbations requiring IV antibiotics and the patient feels symptomatic benefit without improvement in lung function, it may be appropriate to extend a trial for 6 months to see whether there is a reduction in exacerbation frequency.

Continuation of treatment:

After a beneficial trial, the GP should be asked to prescribe DNase on a long-term basis. The CF centre should continue assessment of compliance, symptomatic benefits and side effects on a regular basis. Consideration should be given to a trial of DNase use on an alternate rather than daily basis. This recognizes the balance to be struck between patient effort/time, financial cost and clinical benefit. It is suggested that all patients who have shown benefit from once daily DNase should be trialled on alternate day treatment, while continuing to monitor spirometry and subjective measures.

Frequency of re-assessment after negative trial:

If a trial of DNase shows no benefit, it is reasonable to give a further trial at 3 yearly intervals, or after there has been significant clinical change eg in lung function, sputum production or infection with Pseudomonas aeruginosa.

Adverse effects:

Include chest pain, fever, voice alteration (loss or hoarseness), pharyngitis, rash,

dyspepsia, rhinitis, conjunctivitis, headache. Adverse effects tend to be mild, transient and require no dosing change.

Interactions:
No known drug interactions. Should not be diluted or mixed with any other drugs in the nebulizer, this may inactivate the drug.

Pregnancy & breast feeding:
Teratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Excretion in breast milk unknown/use caution.

References:

1, Cochrane Database CD001127. Updated Feb 2005. 8.36% weighted mean difference (improvement) in FEV_1 at 1 month (7.52% in FVC). 5.8% weighted mean improvement in FEV_1 at 6 month (3% in FVC).

2, Fuchs HJ et al. NEJM (1994); 331:637 968 adults. 24 week trial; mean baseline FEV_1 60% (range 17–140%). 5.8% (+/- 0.7%) relative improvement in FEV_1; (3.5% increase in predicted FEV_1). 22% reduction in exacerbations requiring IV antibiotics (27% vs 22%; p=0.11). 28% age adjusted reduction in exacerbations (p=0.04) (dubious statistical analysis).

3, Quan JM et al. Pulmozyme Early Intervention Trial Study Group. J Pediatrics (2001); 139:813. 474 children (6-10 yrs); 96 week trial; FVC >85% (mean baseline FEV_1 95%). 3.1% (+/- 1.2%; p=0.006) improvement in FEV_1. 34% relative reduction in exacerbations (p=0.048). Spirometry response does not predict patients with fewer exacerbations.

4, McCoy K et al. Chest (1996); 110:889 [Trial in severe lung disease group]. 320 pts (85% adult); 12 week trial; FVC <40% . Improvement in relative FEV_1 (9.4% vs 2.1%; p<0.001);. Improvement in relative FVC (12.4% vs 7.3%; p<0.01). No difference in dyspnoea scores; days of IV antibiotics; hosp stay; 9 vs 6 deaths.

5, Suri R et al. Lancet (2001); 358:1316. 48 children; FEV_1 <70% predicted (mean 48%); 12/52 trial. No difference between daily & alternate-day rhDNase (16 vs 14% increase in FEV_1).

6, Hodson ME et al. Pediatr Pulmonol 2003; 36: 427-432. Analysis of European Epidemiological Registry of Cystic Fibrosis for evidence of benefit in routine clinical practise. Over 2 years, FEV_1 of treated patients were stable (+ 0.3%), while FEV_1 of untreated patients showed decline (–2.3%). Treated patients had 0.25 fewer exacerbations per year. Analysis suggested younger patients were more likely to benefit.

7, Davies J, Trindale MT, Wallace C et al. Retrospective review of the effects of rhDNase in children with cystic fibrosis. Pediatr Pulmonol 1997; 23: 243-248.

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