NHS England

Evidence Review:
Dornase alfa inhaled therapy for primary ciliary dyskinesia (all ages)

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Contents

1. Introduction

Primary ciliary dyskinesia (PCD) is a relatively rare hereditary disorder characterised by chronic infection of the upper and lower airway. Approximately half of patients with PCD will have situs inverses, a congenital condition in which the major visceral organs are reversed. Male infertility is common.

The airway symptoms are caused by impaired mucociliary clearance which results in the accumulation of airway secretions, often containing bacteria and allergens, leading to inflammation and chronic infection. The impaired mucociliary clearance is a consequence of abnormal ciliary beat function. Without appropriate early treatment, progressive chronic lung disease and bronchiectasis develop, and mismanagement of hearing impairment is common. Bronchiectasis can occur in infancy demonstrating the need for early instigation of appropriate treatments. Once irreversible lung damage is established, significant medical input is required with regular hospitalisation for antibiotics, ventilator support with some cases requiring surgical intervention including lobectomy and lung transplantation.

Dornase alfa is a highly purified solution of recombinant human deoxyribonuclease (rhDNase), it reduces viscosity in the lungs and promotes improved clearance of secretions, and is an established inhaled therapy in cystic fibrosis (CF). Individual funding requests are being received for the use of dornase alfa for PCD although its use is off-label for this indication. It is being requested for use in patients who have not responded to conventional treatments with the aim of preventing progressive lung function decline, further lung damage and respiratory failure. Dornase alfa is being requested for short term use (three to six months) to rescue and recover lung function decline in some patients or for use as part of a permanent therapy approach in others.

2. Research questions

Is dornase alfa clinically effective in the treatment of primary ciliary dyskinesia?

Is dornase alfa cost effective in the treatment of primary ciliary dyskinesia?

3. Methodology

Research questions and a search strategy were agreed with key members of the Clinical Reference Group and NHS England Public Health Lead (See Appendix Two). From this a PubMed search was undertaken. In addition, the Cochrane database was searched for systematic reviews. NICE and SIGN were searched for relevant guidance. Relevant papers were identified through abstract review and are summarized in Appendix One. The Clinical Evidence Review has been independently quality assured.

The evidence review did not consider 'grey' literature (i.e., non published, non peer-reviewed) or evidence outside the search strategy.

4. Results

Details of each of the studies reviewed, including a summary of findings, is included in Appendix One.

5. Summary of evidence

There is only low level evidence (Grade 3 studies) on the use of dornase alfa (DNase) in primary ciliary dyskinesia. Three case reports (1995-2007) were identified in the literature search. These three case reports reported improvement in respiratory symptoms (respiratory rate, cough, sputum production), suggestive of improvement in quality of life. No studies used a quality of life index. No studies reported incidence of lung infections.

Two case studies measured pulmonary function at both baseline and post dornase alfa (one reported improvement 11 days post intervention, second study measured lung function 4 weeks post intervention).

No side effects were reported in the cases reports. No data was provided on cost effectiveness.

Appendix One

Grade	Study design and intervention			Outcomes							Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Study Endpoint	Study Endpoint Result	Reference	Complications noted	Benefits noted	Comments
3	Case report	2	DNase	-	Respiratory symptoms	Reported improvement in respiratory symptoms, also noted lung function decreased on ceasing DNase and improved when recommenced (Measured FEV1). Although no baseline lung function test at commencing DNase	-	N/A	N/A	-	El-Abiad, Nisreen M.; Clifton, Shelley; Nasr, Samya Z.. Long-term use of nebulized human recombinant DNase1 in two siblings with primary ciliary dyskinesia. Respir Med 2007; 101(10):247-265.	Nil	Yes Improvement in respiratory symptoms	Case study - observational Worsening of symptoms noted on ceasing Dornase Alfa and improvement of symptoms and spirometry

3	Case report	1	DNase	-	Respiratory symptoms and Changes in lung function (Measured spirometry)	Reported improvement in respiratory symptoms (cough and sputum volume). Also improvement in lung function in 4 weeks from pre-treatment baseline with FEV1 increased by 20% and FVC by 13%	-	N/A	N/A	-	Desai M, Weller PH, Spencer DA.. Clinical benefit from nebulized human recombinant DNase in Kartagener's syndrome.. Pediatr Pulmonol 1995; 20(5):307-8.	Nil	Yes Improvement in symptoms and pulmonary function	Very limited study, n=1, no comparative interventional arm, observational study, not randomised, requires multi centre study

3	Case report	1	DNase	-	Respiratory symptoms, Nocturnal oxygen saturations, and lung function (plethysmography)	Reported improvement in respiratory symptoms (tachypnoea) and improvement in nocturnal oxygen saturations 4 days after commencing DNase. Also reported 11 days after intervention, increase in tidal volume, dec respiratory rate and thoracic gas volume	-	N/A	N/A	-	Ten Berge M, Brinkhorst G, Kroon AA, et al. DNase treatment in primary ciliary dyskinesia – assessment by nocturnal pulse oximetry.. Pediatr Pulmonol 1999; 27(1):59-61.	Nil	Yes Improvement in symptoms and pulmonary function	Case report, observational study - limited as case report as above not a controlled study

4	Other	N/A	DNase	-	-	-	-	-	-	-	A. Barbato, T. Frischer, C. E. Kuehni, D. Snijders, I. Azevedo, G. Baktai, L. Bartoloni, E. Eber, A. Escribano, E. Haarman, B. Hesselmar, C. Hogg, M. Jorissen, J. Lucas, K. G. Nielsen, C. O'Callaghan, H. Omran, P. Pohunek, M-P. F. Strippoli, A. Bush. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children/ ERS Task force. European Respiratory Journal 2009; 34(6):1264-76.	-	-	ERS statement: There are few anecdotal report of benefit for Dornase Alfa in PCD. The role of nebulised rhDNase in PCD patients remains unproven.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	None provided
Updated search terms - Population	Primary ciliary dyskinesia Kartagener syndrome Immotile ciliary syndrome Kartagener triad Kartagener's syndrome Kartagener's triad Polynesian bronchiectasis Siewert syndrome
Updated search terms - Intervention	Dornase Alfa Pulmozyme Recombinant human deoxyribonuclease I Recombinant human DNase rhDNase Dnase
Updated search terms - Comparator	Antibiotics Ventilatory support Neurally adjusted ventilatory assist Proportional assist ventilation Surgical intervention
Updated search terms - Outcome	None
Inclusion criteria	**General inclusion criteria** In order of decreasing priority, the following are included: 1. All relevant systemic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reach 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc) that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 5. Expert opinion

	Specific inclusion criteria
	English language <5 years, <10 years RCTs,SRs,MAs Title/Abstract 3 additional articles per the suggestion of the clinical evidence reviewer: a. Desai M, Weller PH, Spencer DA. Clinical benefit from nebulized human recombinant DNase in Kartagener's syndrome. Pediatr Pulmonol 1995; 20(5):307-8. b. Ten Berge M, Brinkhorst G, Kroon AA, et al. DNase treatment in primary ciliary dyskinesia – assessment by nocturnal pulse oximetry. Pediatr Pulmonol 1999; 27(1):59-61. c. A. Barbato, T. Frischer, C. E. Kuehni, D. Snijders, et al. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children/ ERS Task force. European Respiratory Journal 2009; 34(6):1264-76
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Do not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (except where there are fewer than 10 studies overall) 4. No relevant outcomes 5. Incorrect study type
	Specific exclusion criteria
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