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THE USE OF DNASE IN CYSTIC FIBROSIS

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- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
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FOREWORD

Individuals or small groups in each District Health Authority in Trent have historically considered evidence on the likely effectiveness of new procedures or therapies in conjunction with their cost, making judgements on whether these should be supported. Since all or most Health Authorities face the same issues, there tends to be repetition in analysis and this can be wasteful of scarce professional expertise.

There are national attempts to remedy this situation by providing information on the effectiveness of interventions and these are welcomed. There remains, however, a significant gap between the results of research undertaken and their incorporation into contracts.

Following a request from purchasers, a network has been established in the Trent Region to allow purchasers to share research knowledge about the effectiveness of acute service interventions and to determine collectively their purchasing stance.

SCHARR, the Sheffield Unit of the Trent Institute for Health Services Research, facilitates a Working Group on Acute Purchasing. A list of interventions for consideration is recommended by the purchasing authorities in Trent and approved by NHS Executive Trent. A public health consultant from a purchasing authority leads on each topic and is assisted, as necessary, by a support team from SCHARR which provides help including literature searching, health economics and modelling. A seminar is then led by the consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been approved by NHS Executive Trent.

CONTENTS Page

LIST OF TABLES AND FIGURES

1. INTRODUCTION

1.1 Cystic Fibrosis : incidence and pathology

Cystic Fibrosis is an inherited condition caused by a single gene, autosomal recessive. It affects around one in 2,500 births, although one in 25 of the population are heterozygous carriers. In the recessive autosomal condition it mainly affects the lungs, such that excessively thick bronchial secretions are produced. These are the cause of both frequent infection and subsequently impaired lung function and it is this latter which is the main cause of death.

Pancreatic secretions are also affected - there is an impaired enzymatic secretion leading to gastrointestinal malabsorption. Most cases of Cystic Fibrosis present in childhood.

An estimate of prevalence and survival was carried out in 1991 (1). Table 1 shows that, while the prevalence in children has remained relatively unchanged at about 3,000 in England and Wales, there is an increasing prevalence in adults and therefore an increased all age group prevalence. This increase is predicted to continue over this decade as life expectancy at birth has substantially increased. It is thought that this increased survival is attributable to :

- early diagnosis with improved management of meconium ileus and better management of diet and pancreatic enzyme supplementation;
- routine intensive physiotherapy;
- improved antibiotic therapy (especially anti-pseudomonal);
- specialist Cystic Fibrosis centres (2);
- lung transplantation.

1.2 Prognosis and mortality

It has been shown by Kerem et al (3) that one of the best predictors of mortality is a lung function test known as the forced expiratory volume in one second (FEV_1). These authors showed that the average FEV_1 decline in older children and adults is around 2-4% per annum. When FEV_1 falls to below 30% of the predicted normal, the 2 year mortality

exceeds 50% and at that point the authors recommend that lung transplantation be considered. In very approximate terms the relative risk of death in two years is 2.0 for every decrement of FEV_1 of 10% below predicted value.

Table 1: Prevalence of Cystic Fibrosis in England and Wales

ENGLAND AND WALES				
	AGE			LIFE EXPECTANCY AT BIRTH
Year	<16 years	>16 years	Total	
1980	3,000	800	3,800	20 years
1990	3,300	1,900	5,200	40 years
2000	3,400	>2,600	>6,000	?? years

2. USE OF DNASE IN CYSTIC FIBROSIS : SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Pus, DNA and sputum viscosity

From the 1950s onwards, studies showed that DNA released from white blood cells present in large amounts in infected lung secretions (4). It was thus suggested that bovine DNA splitting enzyme DNase may be effective in reducing the viscosity of infected lung secretions. All of the studies reported, however, were uncontrolled and adverse reactions were also reported.

In 1990 it was reported that recombinant human DNase (rhDNase) could be produced; this breaks down DNA and reduces sputum viscosity (5). A Californian drug company, Genentech, in the early 1990s produced a commercial product of recombinant DNase, known as *Pulmozyme*. An alternative approved name for this drug is Dornase Alpha. It is administered via a nebuliser.

This was licensed and marketed in the UK in 1994. Currently it costs £20 per day for a single 2.5mg dose - equivalent to £7,300 per annum. During the early 1990s phase I, phase II, and phase III trials were carried out. Essentially these phases of clinical trials attempted to answer the following questions:

- Phase I - is it safe?
- Phase II - does it work (using proxy outcomes [in the short term?])
- Phase III - does it improve real outcome in the long term?

2.2 Phase I trials

Some 11 to 16 Cystic Fibrosis patients (18+ years of age) were treated in a placebo-controlled cross-over trial in Maryland (6). Patients received 10 mg twice a day for six days during which time no adverse effects were reported, but there was a 10-20% increase in FEV_1 compared with baseline. There was a return of FEV_1 to baseline after treatment and most patients reported improved breathing.

Similarly, in Seattle 14 adult Cystic Fibrosis patients were treated with 10 mg three times a day for two weeks, followed by a three week gap and then a repeat dose challenge (6). Once again, DNase was well tolerated with no adverse or allergic reactions. There was a 10% improvement in FEV_1 and reduced dyspnoea on a visual analogue scale.

2.3 Phase II trials

Following the successful Phase I trials, two groups carried out longer-term and larger studies. From Seattle, Ramsay et al (8) report a randomised placebo controlled multicentre trial involving 181 Cystic Fibrosis patients aged 8+ years of age. Three dose levels and placebo were given for ten days and the subgroups compared. The only important side effect was upper airway irritation, and in terms of benefit an increase in FEV_1 of 10-15% compared with placebo was observed (with some dose dependence). The FEV_1 improvement was greatest when the disease was worse and FEV_1 reverted to baseline after treatment. In treated patients dyspnoea and well-being improved.

In the UK, Ranasinha et al (9) reported on a double blind randomised control trial of DNase in 71 Cystic Fibrosis patients aged 16+ years of age. These patients received 2.5 mg twice daily or placebo for 42 days. No adverse effects were reported and, although there was a 13% improvement in FEV_1, this time there was no significant change observed in dyspnoea, well being, use of antibiotics or hospital admission. The same group described a longer-term follow-up of 59 of the original 71 patients in the 1993 study; this was now an open-label case series study (10). Patients received 2.5 mg twice daily for six months, followed by a two week "washout". A 13% increase in FEV_1 was observed compared to baseline at first, but, after around a month, this stabilised to a more modest 6% increase. After treatment was discontinued, FEV_1 reverted to baseline. Measurements of dyspnoea mirrored FEV_1 changes, with no change in well-being or symptoms score. The only important side-effect was pharyngitis. In an as yet unpublished report, Shah et al (11) follow the same cohort of patients receiving 2.5mg once daily for a total of 21 months. The FEV_1 continued at around 7% above baseline. There was an increase in patients' weight but no differences in mortality rates from those expected with a group of this composition.

2.4 Phase III trial

Following the Phase II trials which showed an improvement in respiratory function, albeit relatively modest after the initial improvement, a relatively large double blind randomised control trial involving 988 Cystic Fibrosis patients (aged 5+ years) was reported from California (12).

Patients were randomised to receive either 2.5 mg once daily, twice daily or placebo for 24 weeks. The main outcome measure reported by these investigators was investigations needing parenteral antibiotic - these occurred in 20% of those treated with placebo, 22% of those given once daily DNase and 19% of those receiving twice daily treatment. A post-hoc age adjustment to allow for differences between the randomised groups resulted in an increase in the estimate of exacerbation reduction in treated patients. FEV_1 improved overall by 5.8% although, as in Phase II trials, there was a larger increase at first and the response was appreciably variable between patients.

There were small positive changes in symptom score, dyspnoea and well-being but no difference was observed in mortality or major complications. The main side-effect noted was pharyngitis.

A brief and rather inadequately described economic analysis at the end of this trial reported that the cost of DNase was mitigated by around 18-36% by a combination of the lower cost of antibiotic and of fewer days spent in hospital.

2.5 Conclusion on direction of evidence and its quality

This drug has attracted a considerable amount of interest and not a small amount of controversy. On the positive side it is felt that most of the improvement in mortality in Cystic Fibrosis has come by a combination of individually small benefit interventions which together have summed to at least a doubling of life expectancy in recent years. While, for example, the FEV_1 improvement is only modest it must be set against the usual pattern for these patients which is an exorable decline in FEV_1 and an associated increase in the risk of mortality. On the other hand, the drug is expensive, has only been tested for a relatively

short period of time in published data and no evidence of reduced mortality or major complications has been seen.

Table 2: Reactions to published data

Positive and enthusiastic		Negative and cautious
Genentech and Roche - February 1994		***Regional Drug Information Service - May 1994***
"Pulmozyme improves lung function ....." - "..... reduces breathlessness and improves patient's perception of well-being." - "Patients spend less time in hospital, fewer days on parenteral antibiotics and less days off school or work".		Further studies are needed in view of "modest clinical benefits", high cost and the fact that not all will benefit.
Cystic Fibrosis Trust - March 1994		***British Thoracic Society - September 1994***
DNase should only be prescribed by C.F. centres - Guidelines were suggested - DoH should be asked for special funding - some, but not all, will benefit - "it is not a life-saving drug" - further studies and information are required.		"..... we do not feel there is good enough scientific evidence as yet to justify the expense of treatment".
Respiratory Physicians - Autumn 1994		***Drugs and Therapeutic Bulletin - February 1995***
"DNase has been rigorously tested in a large number of patients and clear evidence of benefit has been demonstrated". "5% improvement in respiratory function is a real advantage."		"..... small improvement in lung function and a slight reduction in the frequency of respiratory infections needing parenteral antibiotics. However, it is not clear whether these improvements offer a clinical advantage." "On the evidence available we cannot recommend that Dornase alpha should be added to a formulary."
		Wessex Institute of Public Health Medicine - September 1995
		"marginal benefits of the drug taken together with its high cost do not warrant a headlong rush to use it before the results of further longer term trials are available."

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

The annual cost of treatment is around £7,300 for once daily dosage and £14,600 for twice daily dosage.

In Sheffield there are approximately 60 patients with Cystic Fibrosis. The cost, therefore, of treating only half of these patients would be between £220,000 and £440,000 per annum. A very preliminary look at costs and life year benefits was modelled for discussion at a seminar held on this subject in Trent. An imaginary cohort of 100 patients with Cystic Fibrosis was considered over a ten year period applying the likely DNase changes to FEV_1(i.e. a reduction in FEV_1 per annum of 1.5% compared to 3.0% in the untreated cases). Predicting the effect of these FEV_1 changes on mortality indicates, very approximately, that :

- An extra 130 life years will result at a cost of £5m - i.e. £47,000 per life year.
- This compares, for example, with some of the most expensive interventions, such as haemodialysis for end stage renal failure, the cost of which is about £25,000 per life year.

The graph below (fig.1) gives a very approximate indication of how the survival curves might look in this very approximate model. It should be noted, however, that these predictions are very sensitive to both the time-frame used and the reduction in FEV_1 per annum assumed. In addition, discounting both the costs and benefit tends to increase the costs per life-year. Each one of these issues is addressed below.

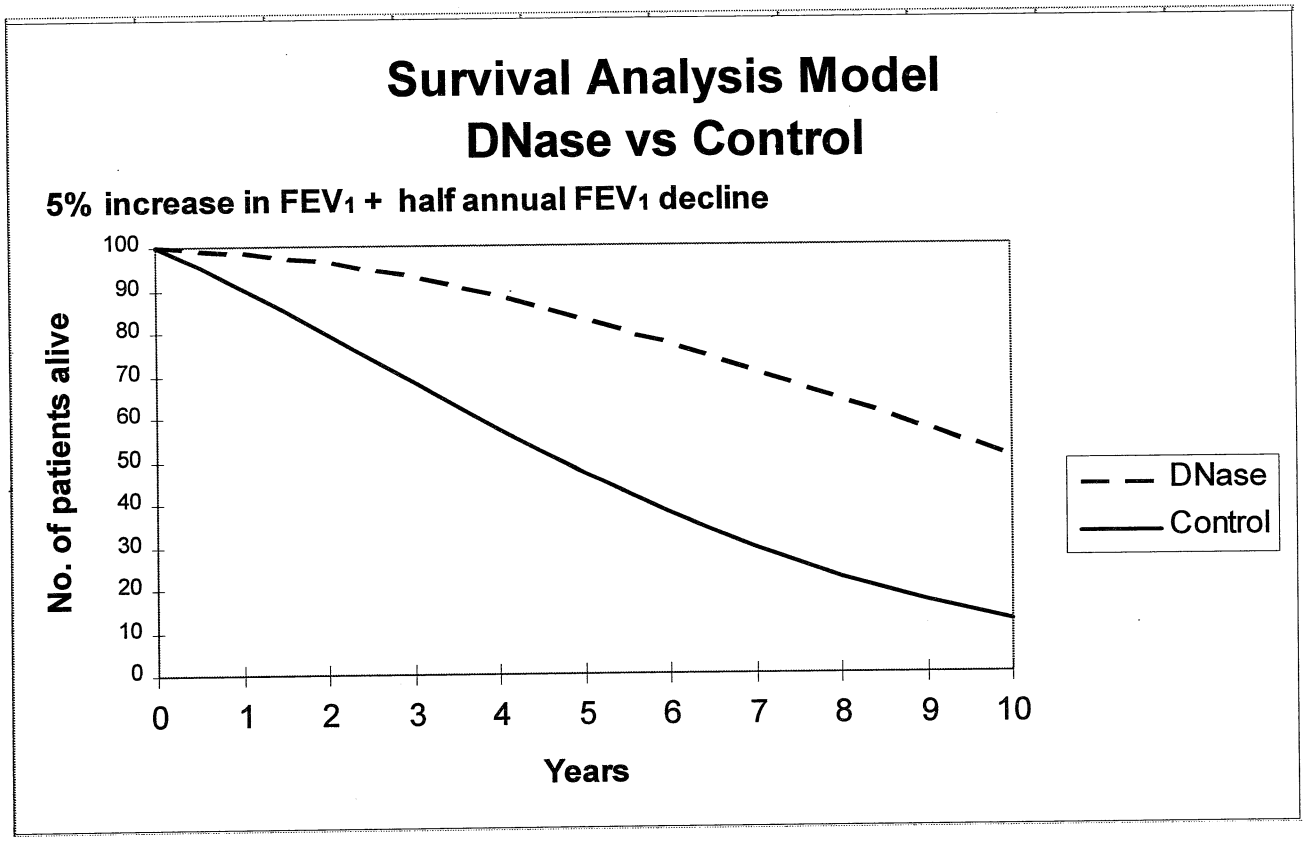
Survival Analysis Model
DNase vs Control
5% increase in FEV1 + half annual FEV1 decline
No. of patients alive
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
Years
DNase
Control

fig.1

Table 3: The cost per life year saved for different time frames and reductions in FEV_1 per annum

TIME FRAME	REDUCTION IN FEV_1 PER ANNUM FOR THE INTERVENTION GROUP		
	1.0%	**1.5%**	**2.0%**
5 YEARS	£ 97,000 (£103,000)	£129,000 (£138,000)	£193,000 (£206,000)
10 YEARS	£ 35,000 (£ 40,000)	£ 47,000 (£ 54,000)	£ 72,000 (£ 83,000)
15 YEARS	£ 23,000 (£ 28,000)	£ 31,000 (£ 38,000)	£ 47,000 (£ 58,000)

The value in parentheses is the cost per life year saved after discounting both costs and benefits at 6% p.a.

i) Time frame

Table 3 illustrates how the cost-effectiveness ratio decreases as the time frame is extended. For example, extending the time frame from 5 years to 15 years decreases the cost-effectiveness ratio dramatically from £129,000 per life year saved to £31,000 per life year saved (assuming the reduction in FEV_1 per annum = 1.5%).

ii) Reduction in FEV_1 per annum

Similarly, varying the reduction in FEV_1 per annum from 1% to 2% results in a substantial increase in the cost-effectiveness ratio. This suggests that more evidence is needed on the benefits of DNase so that a more precise measure of the percentage reduction in FEV_1 per annum can be obtained and hence a judgement about the cost-effectiveness of treatment using DNase can be made.

iii) Discounting

Discounting both costs and benefits also affects the cost-effectiveness ratio. For example, assuming a time-frame of 10 years and a reduction in FEV_1 per annum of 1.5%, discounting both costs and benefits at the 6% level will increase the cost-effectiveness ratio from £47,000 per life year saved to £54,000 per life year saved. This suggests that the later periods of the intervention are the most cost-effective, but discounted the heaviest.

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4. OPTIONS FOR PURCHASERS AND PROVIDERS

Several possible options were presented and discussed at the Trent Institute Working Group on Acute Purchasing Seminar in May 1995. Those presented and discussed are as follows:

i. That there should be no extra funding, at least until longer-term studies demonstrate clear evidence of improved outcome, particularly mortality.
ii. Providers should be encouraged to reallocate resources internally from less cost-effective interventions to allow prescribing to take place but without additional purchaser funds.
iii. Purchasers should agree to fund in the context of formal (large/multi-centre) clinical trials.
iv. Funding should be agreed for limited use:
    - In Cystic Fibrosis centres
    - Within agreed clinical guidelines for use
    - With allowance for reduced cost of in-patient care and costs of parenteral antibiotics.
v. Funding should be agreed for widespread use, but with the assurance that the results of audit of use are provided.

5. DISCUSSION AND CONCLUSION

After discussion at the Trent Seminar between representatives of purchasers and Cystic Fibrosis care providers it was agreed to recommend option 4 from those listed above - that is that funding should be agreed for limited use within Cystic Fibrosis centres, within agreed clinical guidelines and with allowance for reduced cost of in-patient care and parenteral antibiotics.

To this end a matrix setting out details of this agreement was produced in the form shown below.

6. USE OF DNase in CYSTIC FIBROSIS: SUMMARY MATRIX

PATIENT GROUP	PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)	ESTIMATED FUTURE ACTIVITY	OPPORTUNITY FOR COST SAVING	AUDIT POINTS	EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT	COST-EFFECTIVENESS
Adults and children (5 years or older) with Cystic Fibrosis and with agreed criteria for treatment	**Criteria for starting treatment:** • FEV_1 < 70% **and** • Producing a lot of sputum **and** • Show FEV_1 and/or symptomatic improvement within one month **and** • Treatment within/supervised by a Cystic Fibrosis centre **and** • More than one exacerbation of respiratory infection requiring IV antibiotics in last 12 months **Criteria for continuing treatment:** • FEV improvement within one month of treatment (at least 5-10%) and/or significant improvement in respiratory symptoms and a decrease in respiratory infection) • Treatment within/supervised by Cystic Fibrosis centre. • Consider shared care with GPs after 4 weeks of treatment - see draft protocol **Criteria for discounting treatment:** • Failure to demonstrate a significant improvement • Poor compliance • Allergic reaction	1/3 of affected adults - approx. 6 in a district of 500,000 1/5 - 1/6 of affected children approx. 6-7 in a district of 500,000 Cost, assuming above, approx. £90,000 per annum	1. Reduced use of antibiotic treatment 2. Reduced hospital admissions [3. *Reduced use of oxygen therapy in other patient groups - cost release implications*]	1. FEV_1 improvements on treatment 2. Exacerbations needing antibiotics 3. Adherence to guidelines for use 4. Mortality/ survival rate analysis	1. Respiratory function improvement (or slower decline) 2. Symptomatic improvement 3. A projected/modelled gain of 20 extra life years in the treated group (6 children, 6 adults) for 10 years of treatment (an approximate estimate only)	Assuming: i) the time frame = 10 yrs ii) the reduction in FEV_1 per annum using DNase = 1.5% then the undiscounted CE ratio = £46,919 per life years saved, and the discounted CE ratio = £54,026 per life years saved The cost-effectiveness ratio is sensitive to : 1. the time frame 2. the reduction in FEV_1 per annum using DNase NOTE: these figures do not include possible cost savings

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