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CORRESPONDENCE

Placebo-controlled n-of-1 trials in cystic fibrosis

To the Editor:

We have read, with interest, the paper about targeted introduction of recombinant human deoxyribonuclease (DNase) through n-of-1 trials in cystic fibrosis by BÖLLERT *et al.* [1]. We too recognize the significant burden that nebulized DNase presents to the prescribing budget, the diversity of individual response to treatment and the difficulty in identifying those patients who are likely to benefit most from DNase.

In order to introduce therapy in a controlled fashion in our adult centre, and to ensure that the costs of the drug are met by the purchasing Health Commissions we felt that it was important to formally assess benefits in terms of exercise tolerance and quality of life as well as lung function. The primary aim was to ensure that both clinician and patient concurred that DNase produced significant change in any or all three of these parameters before long term therapy was initiated. In conjunction with the Cambridge and Huntingdon Health Commission, we set up an n=1 individual, double blind, placebo controlled crossover study of nebulized DNase before establishing a patient on therapy. It was agreed that if a patient was classified as a responder at the end of this trial, the prescribing costs would be met by the purchasing Health Authorities.

Following a 2 week run-in period to confirm stable clinical condition and a test dose in hospital, patients received 6 weeks′ therapy with placebo (identically packaged normal saline) or DNase. After a 2 week washout they then swapped to the alternative therapy for a further 6 weeks and were then followed-up 2 weeks after completion of therapy. At each time point on the trial, lung function, quality of life and exercise tolerance were measured.

Thirteen patients started on the study but three experienced bronchoconstriction (2 on first dose of DNase and 1 after a week of DNase) and thus were excluded from the trial. Hence it is important that first doses are given in Hospital and spirometry should be measured pre- and post-dose.

Of the 10 evaluable patients, 5 patients were classified as responders on the basis of having a >5% increase in percentage predicted lung function relative to placebo. In all cases there was patient and physician consensus with this conclusion and these patients were commenced on regular DNase therapy. Exercise tolerance (12 min walk) and quality of life data were not particularly useful in picking out responders, however, there was a significant correlation between fatigue as measured by the Chronic Respiratory Questionnaire [2] and changes in forced expiratory volume in one second (FEV_1) ($p=0.03$).

In all cases there was patient and physician agreement with the lung function data (consensus before unblinding) thus questioning the relevance of the placebo arm of the trial. Given the costly and laborious nature of a double blind, placebo controlled trial we have decided to disband the placebo arm and initiate DNase therapy in our adult patient group with a 6 week evaluation period. We chose 6 weeks of therapy in an attempt to include as many patients as possible who would benefit from DNase as previous studies have suggested a gradual improvement in lung function over ~3 months [3]. Nonresponsiveness to a 6 week course of DNase does not exclude a future long term benefit.

S. Webb, P. Tansey, H. Brown, A. Jackson, D. Bilton
Adult Cystic Fibrosis Centre, Papworth Hospital, Papworth Everard, Cambridge, CB3 8RE, UK. Fax: 44 1480 831315.

To the Editor:

The recent article on recombinant DNase in cystic fibrosis [1] was very interesting. We note that if this was being planned in our city it would need a detailed protocol and full scientific and ethical review.

The authors point out that studies which include large numbers of subjects may achieve statistical significance but aggregate reporting of data may suggest only small improvements of questionable clinical significance. Aggregate reporting may conceal the presence of large individual variations. Clinicians may have problems in identifying which subset of patients may derive benefits. Also a new treatment may lead to high expectations from both patients and professionals and high emotional tension leading to unreliability in subjective assessment. Desirable end-points of treatment may also vary. For example, the authors included objective measures such as forced expiratory volume in one second (FEV_1) post physiotherapy, but excluded after analysis other objective measures such as peak flow. The authors included subjective measures such as symptom score for breathlessness and cough but excluded after analysis and other self-rated scores such as sputum clearance and measures of well-being. Factors were excluded after analysis because they had not changed differently in response to placebo and deoxyribonucleic acid (DNA).

An n-of-1 study allows patients to serve as their own controls and may reduce or remove inter-subject variability. In determining the end-point, negotiation between the physician and patient on an acceptable outcome is important. It may be difficult to differentiate an n-of-1 study with many subjects from any other placebo controlled study. The distinction is important: is the study to help one patient or to draw general conclusions? Is this quality improvement or research? If research, the process of design, reviews by regulating authorities and consent by the subject is important. It is also important to know how the study was funded, and who paid for the drug supplies.

The authors state "Since the intention was directed use of a licensed preparation it was considered inappropriate to seek ethics committee approval". What does "inappropriate" mean and to what does it refer? Does it mean "unnecessary"? Does it refer to "licensed"? Do studies of licensed products not need approval or full informed consent?

The language used by the investigator such as "study subjects" implied that it is felt that this was research. The phrase "directed use" implies that there may have not been choice for the subjects/patients. What exactly does the phrase "verbal consent" imply in this context? Was there an agreed script for the verbal consent? Was written material available for the patients or guardians?

There are transatlantic differences in the regulation of research, but the issues we have identified here on the approval of research and on informed consent are general issues worthy of comment.

I. Mitchell*, C.J. Doig
*Dept. of Paediatrics and Division of Critical Care, Faculty of Medicine, University of Calgary, 3330 Hospital Drive N.W., Calgary, Alberta, Canada, T2N 4N1. Fax: 14032838524.

From the authors:

We welcome the comments from S. Webb and colleagues regarding their protocol for the targeted introduction of nebulized deoxyribonuclease (DNase) in cystic fibrosis (CF) patients. We agree that therapy should be introduced through a randomized placebo-controlled n-of-1 assessment. However we disagree with their conclusion to abandon the placebo limb and limit the assessment to change in lung function after having studied only 10 patients. The end-point of >5% increase in percentage predicted forced expiratory volume in one second (FEV_1) is potentially unreliable. This criterion does not take into account, a) the day-to-day variability in FEV_1 of ~160 mL (95% confidence interval (CI)) regardless of the magnitude of FEV_1 [4] and b) the absolute value of the baseline FEV_1. Patients with a low FEV_1 can easily achieve an increase of >5% by chance (which in absolute figures will be <160 mL). Counting such patients as responders might have contributed to the response rate of 50% (5 out of 10 patients) in the Papworth group. In contrast to S. Webb and colleagues we did find, in a larger group (52 patients), significant improvements in O_2 saturation at rest and after exercise and in work performed after DNase although the magnitude of the changes was smaller than for FEV_1. Symptom scores also revealed significant improvements in cough and breathlessness [1]. Analysis of our placebo-control data showed that, if only FEV_1 were used, 1 in 16 patients would be scored as having responded to treatment after receiving only saline. This compares with none of 32 patients showing a false positive response to placebo using the whole protocol including exercise and symptom recording. We conclude that FEV_1 testing alone is insufficient to determine responder/nonresponder status.

S. Webb and colleagues have based their chosen treatment period of 6 weeks on a study [3] in patients with severe pulmonary disease forced vital capacity ((FVC) <40% predicted) for which DNase is not licensed. Previous phase II studies have shown that the maximum effect of DNase on FEV_1 occurs within 10 days with a subsequent approximate halving of the benefit after 2–4 weeks [5, 6], In our experience, many patients dislike prolonged assessments and others are not stable enough to evaluate in this way (frequent exacerbations). Therefore we feel that an active treatment period of 2 weeks is optimal. It is also important, in our opinion, to persist with double blinding and placebo-controlled periods to obviate bias given the high expectations in patients and carers. We agree that the assessment process is laborious but view our protocol as one model to obtain objective data in order to target treatment to those patients who are most likely to benefit.

The pertinent comments of I. Mitchell and C.J. Doig are correct in pointing out the unusual ethical dilemmas pertaining to reporting of such "n-of-1" studies, in particular the definition of what is research and what are the appropriate limits to the processes of ethics review and formal consent. We believe many of the points they raise are of great interest and at present unanswered. The Scottish Cystic Fibrosis Group discussed the issue of ethics at the initiation of our project and as we stated, we reached the conclusion that since the intention was directed use of a licensed preparation it was considered inappropriate to seek ethics committee approval. We draw an analogy with the common practice (at least in the UK) of performing a "steroid trial" (*e.g.* 2 week trial period of prednisolone therapy with peak flow monitoring) in patients with airflow limitation to detect steroid responsiveness. In both cases the intention is to investigate whether that individual responds to that licensed drug, given for a standard indication. In the UK it would not be standard practice to seek ethics approval nor formal written consent for a steroid trial, although full explanation of the purpose and risks of such a trial would of course be given routinely. We did indeed provide patients and their general practitioners with extensive verbal and written information on the nature of our n-of-1 DNase assessments, and the response was very favourable from all concerned. By "directed use" we mean only that we made an attempt to target therapy where maximum benefit could be demonstrated, not that choice was denied to patients. In our experience, the great majority of patients understood what we were trying to do, agreed to participate and accepted the outcome of the assessment.

It is of course important to prevent commercial pressures from influencing such assessments. As indicated in our paper, the trial medication was funded from government (National Health Service) funds, but we did receive help from the manufacturer only for the additional costs of blinding and packaging the trial materials.

When information of this type (aimed at helping individuals) is collated from a number of patients into a paper, does it then become research? Here we think opinions will differ. It is our opinion that the main purpose of ethical review of research projects is to protect patients from potential harm or distress from untried clinical measurements or medications. In our DNase project, no novel clinical measurements were used nor were any drugs administered except for their standard indications. For many years, doctors have pragmatically tried the effect of drugs in individuals in their everyday clinical practice, commonly withdrawing treatment if no effect is observed. The n-of-1 methodology seems to us to offer the opportunity to refine and render more objective this common practice. Finally, the purpose of each patient's participation in our protocol was to determine as accurately as possible their own optimal clinical management. It is important to distinguish this activity from a conventional clinical trial involving the introduction of a novel compound or measurement with the intention of detecting an average effect in a group of individuals. In the latter case individual patients' of the trial has little relevance to their individual clinical management but instead contributes towards a common altruistic research goal. It could be argued, therefore, that different ethical principles should apply and ethics review of the latter type of research protocol is undoubtedly appropriate.

J.A. Innes, F.G.E. Böllert
Respiratory Unit, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, UK. Fax: 44 1313433989.

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