



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Longitudinal assessment of biomarkers for clinical trials of novel therapeutic agents

Citation for published version:

Alton, EW, Boyd, C, Cunningham, S, Davies, JC, Hyde, SC, Innes, JA, Gill, DR, Greening, A, Griesenbach, U, Higgins, T, Porteous, DJ & UK CF Gene Therapy Consortium 2010, 'Longitudinal assessment of biomarkers for clinical trials of novel therapeutic agents: the run-in study' Thorax, vol 65, no. Suppl 4, S18, pp. 298-298., 10.1136/thx.2010.150912.18

Digital Object Identifier (DOI):

[10.1136/thx.2010.150912.18](https://doi.org/10.1136/thx.2010.150912.18)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Preprint (usually an early version)

Published In:

Thorax

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Abstract S16 Table 1 Diagnostic performance of %VLF and ODI >3% for detection of SDB in CHF patients

	%VLF	ODI>3%
Sensitivity	0.53	0.97
Specificity	0.44	0.32
Positive predictive value	0.45	0.53
Negative predictive value	0.51	0.94
Positive likelihood ratio	0.94	1.42
Negative likelihood ratio	1.08	0.08
Area under receiver operating characteristic curve	0.49	0.92

Funding This study was funded by the British Heart Foundation.

S17 A PILOT STUDY OF THE PREVALENCE OF SLEEP DISORDERED BREATHING (SDB) AND NOCTURNAL HYPOXIA IN SYMPTOMATIC ADULTS WITH SICKLE CELL DISEASE (SCD) AND ITS RELATIONSHIP WITH DISEASE SEVERITY

doi:10.1136/thx.2010.150912.17

¹P Murphy, ²R Dillon, ³A J Williams, ²J Howard, ¹N Hart. ¹Guy's & St Thomas' NHS Foundation Trust and Kings College London NIHR Biomedical Research Centre, London, UK; ²Department of Haematology, Guy's & St Thomas' NHS Foundation Trust, London, UK; ³Lane Fox Respiratory Unit, Guy's & St Thomas' NHS Foundation Trust, London, UK

Introduction There are few effective therapies available for the long-term management of the cardiac and renal sequelae of SCD. Identifying reversible factors, which exacerbate disease severity, would facilitate development of new therapies or novel applications of established treatments. Nocturnal hypoxia (NH) merits investigation as a disease modulating factor as it is established that hypoxia promotes polymerisation of sickle haemoglobin and this is reversible with oxygen therapy (Noguchi *et al*, 1993). Although NH is common in children with SCD and is associated with poor outcome, similar data for adults with SCD are lacking. This is the first study to determine the prevalence of OSA and NH and quantify the severity of NH in adults with SCD. In addition, we investigated the correlation between the degree of NH and organ dysfunction.

Method Patients attending SCD clinic had an Epworth sleepiness score performed. Patients with either an ESS ≥ 10 or symptoms suggestive of SDB were offered nocturnal oximetry. Nocturnal oximetry findings were objectively scored and compared with the detailed clinical datasets collected at regular clinic attendances. OSA was defined as 4% oxygen desaturation index (4% ODI) of >10 events/h and NH was defined as >30% total sleep time (TST) with SpO₂ <90%.

Results 93 patients were screened. 34 had ESS ≥ 10 or clinical symptoms suggestive of SDB. 22 underwent nocturnal oximetry; mean ESS 12 \pm 4, clinic SpO₂ 96 \pm 4%, 4% ODI 8 \pm 6 events/h, nocturnal SpO₂ 91 \pm 4%, %TST SpO₂ <90% 43 \pm 41%. Prevalence of OSA and NH was 59%. The degree of nocturnal hypoxia was correlated with urine protein:creatinine ($r=-0.35$, $p=0.02$), elevated pulmonary artery systolic pressure ($r=-0.71$; $p=0.0001$) and prevalence of priapism ($p=0.004$). There was no difference detected in frequency of painful crises or hospital admission in patients with significant NH compared to those without NH.

Conclusion This small pilot study showed that OSA and NH had a prevalence of 59% in symptomatic adult SCD patients. These data have demonstrated a correlation between the severity of nocturnal hypoxia and pulmonary hypertension, renal impairment and priapism. These observations have not previously been reported. The strength of these correlations could suggest a causal relation-

ship, although this needs to be confirmed in a larger prospective trial. Future studies should investigate the relationship between OSA, nocturnal hypoxia and organ dysfunction and need to be focussed on interventions such as nocturnal oxygen and continuous positive airway pressure.

New assessments in cystic fibrosis

S18 LONGITUDINAL ASSESSMENT OF BIOMARKERS FOR CLINICAL TRIALS OF NOVEL THERAPEUTIC AGENTS: THE RUN-IN STUDY

doi:10.1136/thx.2010.150912.18

¹E W F W Alton, ²C Boyd, ³S Cunningham, ¹J C Davies, ⁴S C Hyde, ²J A Innes, ⁴D R Gill, ²A Greening, ¹U Griesenbach, ¹T Higgins, ²D J Porteous. ¹Department of Gene Therapy, Imperial College, London, UK; ²Western General Hospital, Edinburgh, UK; ³The Royal Hospital for Sick Children, Edinburgh, UK; ⁴Gene Medicine Research Group, Oxford University, Oxford, UK

We will be undertaking a phase IIB clinical trial of repeated application of liposome-based gene therapy over a one year period in approximately 100 CF patients (Multidose Trial). In preparation for this, we sought to address two key questions. Firstly, could we define the optimal set of patients in which the therapy could both be delivered (good access to the airways via nebulisation), and in whom any therapeutic effect was measurable (one or more abnormal measures of lung disease). Secondly, in this set of 'can deliver—can measure' patients, which biomarker(s) could be powered to be the primary outcome measure for the trial. To address both questions, we undertook a study (Run-in), cross-sectionally assessing 'can deliver' and longitudinally assessing a large set of candidate biomarkers for 'can measure'. 192 patients from age 10 upwards, with FEV₁ >40% were enrolled at two clinical centres; 154 of these remained in the study after four visits spaced at approximately 4–5 month intervals. Biomarkers assessed cross-sectionally included radionucleotide deposition scans, CT and mucociliary clearance. Longitudinal biomarkers included a large series of serum, sputum and exhaled breath inflammatory markers, lung physiology, exercise-related assays and quality of life assessment. 12 patients were judged too severe for adequate delivery and were excluded. A shortlist of 4 biomarkers was generated based on a) showing a CF/non-CF difference, b) response to course of intravenous antibiotics, and c) coefficients of variation. These four were matched against the remaining 142 patients, and a further seven patients excluded in whom none of these short listed biomarkers was abnormal. 89 patients (3 or 4 biomarkers abnormal) have been definitely included to progress into the Multidose Trial, and a further 46 (1 or 2 biomarkers abnormal) are awaiting the final primary outcome selection. The Run-in study has, therefore, been able to a) select a cohort of 'optimal' patients in which to assess gene therapy and b) provide an indication of which may be the more useful biomarkers to use in phase IIB clinical trials of novel therapeutic agents.

S19 REAL TIME PCR IN THE IDENTIFICATION AND MANAGEMENT OF ASPERGILLUS IN CF

doi:10.1136/thx.2010.150912.19

¹C G Baxter, ²A M Jones, ²A K Webb, ¹D W Denning. ¹University Hospital of South Manchester, Education and Research Department, Manchester, UK; ²Manchester Adult CF Unit, Manchester, UK

Purpose The reported prevalence of *Aspergillus fumigatus* in CF sputum varies widely from 12 to 57%. While patients with ABPA are routinely treated with antifungals, it is not known whether colonised



S18 Longitudinal assessment of biomarkers for clinical trials of novel therapeutic agents: the run-in study

E W F W Alton, C Boyd, S Cunningham, et al.

Thorax 2010 65: A11

doi: 10.1136/thx.2010.150912.18

Updated information and services can be found at:

http://thorax.bmj.com/content/65/Suppl_4/A11.2

These include:

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Clinical trials \(epidemiology\)](#) (375 articles)

[Drugs: infectious diseases](#) (685 articles)

Notes

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>