A turnover longitudinal model for the analysis of FEV1 changes in COPD

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Introduction

FEV1 is the most commonly used endpoint for the assessment of treatment response in chronic obstructive pulmonary disease (COPD). In this investigation the longitudinal measures of FEV1 over one year are used to describe disease progression in patients assigned to a placebo arm in clinical trials. A parametric approach is used which assumes the contribution of a negative feedback mechanism to explain changes in lung function. The objective of this approach is to explore how differences in baseline conditions and lung capacity alter FEV1.

Disease progression as a negative feedback model

The disease status, as assessed by FEV1 is presented as S in Figure 1A. The magnitude of S is determined by a physiological turnover rate (Kin/Kout).

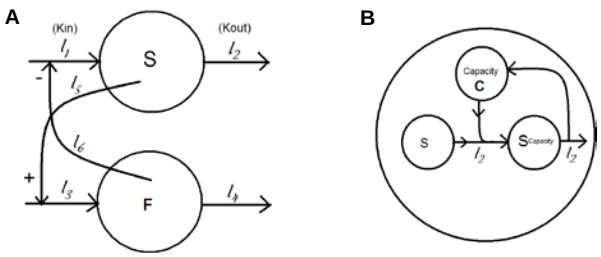

Figure 1. (A) An indirect model describing the decrease in FEV1 over time. It is assumed that the disease is controlled by a hypothetical state **F**, which affects Kin. FEV1 at baseline is defined by the ratio Kin/Kout. **(B)** A linear model for disease status S is further parameterised as a non-linear turnover rate with capacity (C), S is FEV1. (Post et al, *Pharm. Res.* **22**:1038-48, 2005)

The change from baseline FEV1 (**ΔS**) can be described by a second order differential equations in only **ΔS** with Kin (l_1) eliminated under the steady state assumption (input = output).
(Ackerman et al, *Phys. Med. Biol.* **9**:203-13, 1964).

$$\frac{d^2\Delta S}{dt^2}+\frac{d\Delta S}{dt}(l_2+l_4)+\Delta S(l_2l_4+l_5l_6)=0$$

Or in standard second order differential equation form (Martin Healey, Butterworth-Heinemann 1975):

$$\frac{d^2\Delta S}{dt}+\frac{d\Delta S}{dt}(2\varsigma\omega_n)+\Delta S\omega_n^2=step\,\omega_n^2$$

The solution of the above equation for $\zeta<0$ following a step input is:

$$\Delta S=step[1-e^{-\zeta\omega_n t}(\cos(\omega t)+\frac{\zeta}{\sqrt{(1-\zeta^2)}}\sin(\omega t))]$$

The ω_n and ζ were estimated for each individual with four or more samples using nonlinear least square method (nlm()). The Kout (l_2) estimate is assumed to be $\omega_n\zeta$. The accuracies of estimates were within 5% (CV). The Kout (/week) estimates were regressed against the subject specific covariates (Table 1).

A linear disease progression S was assumed with model parameterisation according to a nonlinear turnover mechanism (Figure 1 B). The steady state characteristic of the model is:

$$l_2x_2=\frac{l_2Cx_1}{x_1+C}$$

$\boldsymbol{X_1}$ is **S** (FEV1) & $\boldsymbol{X_2}$ is **S**capacity at a given disease status and **C** is Capacity. (Boroujerdi et al, *Am. J. Physiol.* **268**: E766-E774, 1995)

Results

Table 1

Intercept (CV%)	2.864 (7.44%)	P<0.001
Gender	-0.278 (18.34%)	P<0.001
Ex-smoker (compared to smoker)	-0.441 (10.88%)	P<0.001
Non-smoker (compared to smoker)	0.994 (12.77%)	P<0.001
Age	-0.005 (63.82%)	P=0.067
BMI	0.006 (66.66%)	P=0.171

The lung capacity is initially assumed to have the same value as initial FEV1. The inputs (Kin) to the disease progression models were computed by forward simulations, that is calculating fold (or %) changes in Kin and the lung capacity (C) such that it mimics the observed FEV1. The pattern of Kin was assumed to change discreetly relative to the observed FEV1 values, namely +1 (increase) -1 (decrease) 0 (no change). NONMEM was used to estimate the population magnitude of fold step changes (Table 2).

Figure 2 shows the goodness of fit for the proposed linear model. The goodness of fit for different lung capacities including baseline FEV1, 2 L, 3 L and 4 L were similar.

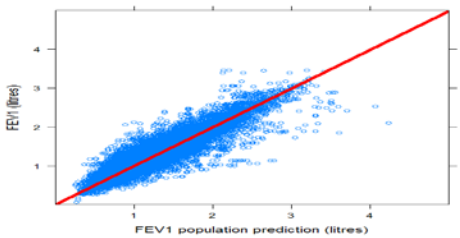

Figure 2. The goodness of fit plot for the linear model.

Table 2

Mean (SE)	Fold step changes in lung capacity and magnitude of Kin.	ETA, the SQRT of η represents IIV
Linear Model	0.0570 (0.00099)*	0.196 (0.0300)
Nonlinear model C = baseline FEV1	0.0688 (0.00006)	0.324 (0.083)
Nonlinear model with C= 2 liters	0.0644 (0.00154)	0.236 (0.044)
Nonlinear model with C=3 liters	0.0600 (0.00319)	0.233 (0.115)
Nonlinear model with C= 4 liters	0.0584 (0.00133)	0.218 (0.0348)

***for the linear model only the Kin is changed.

Conclusions

The nonlinear model for disease progression provides a preliminary basis for the evaluation of placebo response in clinical trials in COPD. This type of parameterisation can also be used to explore the effects of different mechanisms of action on FEV1. We have also identified patient specific characteristics that determine the elimination rate constant (Kout) for change in lung function.

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